EXHIBIT N

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
MDL No. 2875

IN RE: VALSARTAN, PRODUCTS LIABILITY LITIGATION

TESTIMONY OF:

Stephen Hecht, Ph.D.

August 17, 2021
9:00 a.m.

TRANSCRIPT of the stenographic notes of the video recorded proceedings in the above-entitled matter, as taken by and before Sara K. Killian, a Registered Professional Reporter, Certified Court Reporter and Notary Public, remotely via Zoom videoconferencing.

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R E Q U E S T S:

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THE VIDEOGRAPHER: Good morning. We are going on the record at 9:13 a.m. on August 17, 2021. This is media unit one of the video recorded deposition of Steven Hecht, PhD in the matter of the valsartan, losartan case.

My name is William Miller from the firm Veritext Legal Solutions. I'm the videographer. The court reporter is Sara Killian from the firm Veritext Legal Solutions.

All counsel is noted on the stenographic record.

Will the court reporter please swear in the witness and we can begin?

S T E P H E N H E C H T, P h D, after having first been duly sworn, was examined and testified as follows:

MR. TRISCHLER: Dr. Hecht, good morning.

THE WITNESS: Good morning.

MR. TRISCHLER: Before we begin, I just want to confirm on the record an agreement that Mr. Slater and I reached before the beginning of this deposition.

This is the time and place set for the deposition of Dr. Steven Hecht. Dr. Hecht issued a report dated July 6th, 2021 and we're here today to take his deposition on issues relating to causation opinions that Dr. Hecht has or may have or wishes to testify about in connection with the valsartan multi-district litigation.

The report of July 6, 2021 includes opinions and potential areas of testimony that go beyond the issue of causation and get into what I would consider to be other liability issues.

I believe the agreement of the parties is that any inquiry of Dr. Hecht on those issues unrelated to causation will be deferred until a later period of time in connection with this multi-district litigation. My deposition of Dr. Hecht and the defendant's deposition of Dr. Hecht today will be limited to causation opinions.

Is that fair, Mr. Slater?

MR. SLATER: Yes. This deposition will not address liability, but will address general causation.

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MR. TRISCHLER: Understood and agreed.
Thank you.
EXAMINATION BY
MR. TRISCHLER:
Q. Dr. Hecht, as I mentioned just a moment ago, my name is Clem Trischler. I'm an attorney. I represent the Mylan defendants and the Defendants' Executive Committee in the valsartan multi-district litigation that's pending in the United States District Court for the District of New Jersey.
You have been identified and disclosed as an expert witness on behalf of the plaintiffs in this litigation.
Are you aware of that?
A. Yes.
Q. Obviously, we're gathered to take your deposition on causation issues relevant to this litigation. I take it that you've given deposition testimony before?
A. Yes.
Q. Given that fact, I'll refrain from going into a detailed discussion of what the deposition process is, but suffice it to say

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myself and perhaps some other lawyers are going to be asking you questions today and the answers that you are providing are answers under oath and under penalty of perjury.
Do you understand that?
A. Yes.
Q. I presume then that the answers that you provide to my questions today will be honest and truthful and to the best of your ability?
A. Yes.
Q. Tell us your full name, sir.
A. Stephen Samuel Hecht.
Q. What's your professional address, Dr. Hecht?
A. Masonic Cancer Center, University of Minnesota, Minneapolis, 55455.
Q. Where are you physically located today as you give your deposition?
A. I'm in the Cancer and Cardiovascular Research Building on the university campus.
Q. And the university campus being the campus of the University of Minnesota?
A. Yes.
Q. Is anyone in the room with you as you give your deposition testimony today?

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A. No.
Q. Are you using a laptop or a desktop computer to participate in this deposition?
A. It's a laptop.
Q. Do you have any other electronic devices with you in the room as you give this deposition other than the laptop on which you're using to communicate with me?
A. Yes. I have my desktop and my phone.
Q. Would it be possible for you to turn your desktop and phone off during the deposition?
A. I can. I was going to use the desktop to view any of the papers that we're going to discuss under sender say. I was given a link to Novac Trial Services that would have the -- a lot of the documents, so I thought that would be convenient to look at, but I can turn it off.
Q. Well, that's -- that's all right.
What I want to make sure is that you're not receiving communications from any source on other electronic devices during the time of the deposition.
A. No.
Q. All right.
What's your occupation?

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A. I'm a professor. Walin Professor of Cancer Prevention, University of Minnesota.
Q. You indicated in response to one of my earlier questions that you were, in fact, retained by the plaintiffs in the valsartan litigation.
True?
A. Yes.
Q. When were you initially retained to work for the plaintiffs in this litigation?
A. I don't have the exact date. It's about two years ago.
Q. I was provided with some of your invoices within the last couple of days and I'll represent to you that the earliest entry that I saw on your invoices was September 4, 2019.
A. Yes, that sounds about right.
Q. So would that entry refresh your recollection as to the approximate period of time when you were initially retained in this litigation?
A. About two years.
Q. So about two years ago would be September 2019; true?
A. Yes.

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Q. Who initially retained you?
A. Mr. Slater.
Q. When you were retained by Mr. Slater, were you asked to analyze data and provide an opinion on whether levels of NDMA and NDEA observed in valsartan-containing medication was capable of causing cancer in humans?
A. Yes.
Q. Did you attempt to answer that question in the July 6, 2021 report that's been filed in this case?
A. Yes.
MR. TRISCHLER: I'm going to mark as Exhibit 1 to the deposition a copy of your July 6th, 2021 report.
(Whereupon, Exhibit 1 was marked for identification.)
Q. Do you have that with you, Dr. Hecht.
A. Yes, I do.
THE VIDEOGRAPHER: Counsel, would you like me to pull that up on the screen?
MR. TRISCHLER: If need be. It might -- let's --
MR. SLATER: He has it in hard copy, I think.

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MR. TRISCHLER: That's why I'm asking if he has it. I'd rather just work with the doctor if he has it.
Q. You have the report that we marked as Exhibit 1, sir?
A. Yes.
Q. All right.
Is that your signature that appears on the first page of that report?
A. Yes.
Q. Did you prepare this report?
A. Yes.
Q. Is it the product of your work?
A. Yes.
Q. Did anyone assist you in the preparation of this report?
MR. SLATER: Clem, objection.
Are you trying to get into areas that are obviously covered by work product privilege? I mean, the preparation of the report is work product. Drafts are the not discoverable, so I'm not sure where we're going with this.
MR. TRISCHLER: I didn't ask about drafts. I asked if anyone helped him with

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the report. It could have been his wife, it could have been an associate professor. It could have been anyone, Adam.
MR. SLATER: So anyone other than a lawyer?
I'll allow him to answer.
Q. Did anyone assist you in the preparation of this report, sir?
A. Yes. I was assisted by Mr. Slater.
Q. I'm not interested in what assistance Mr. Slater may have provided, so other than Mr. Slater, did anyone assist you in the preparation of this report?
A. No.
Q. Did anyone write any sections of this report for you?
A. No.
Q. In the conclusion to your report that appears on page 27, you write "These nitrosamines in valsartan-containing medication posed an unacceptable risks of causing or substantially contributing to the causation of cancer for those ingesting the valsartan."
Did I read that correctly?
A. Presumably.

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Q. Is there a difference in your mind between an exposure that creates an unacceptable risk of contributing to cancer causation and an exposure that definitely causes cancer?
MR. SLATER: Objection to the form of the question.
You can answer.
A. Repeat the question.
Q. Sure.
Is there a difference in your mind between an exposure that creates an unacceptable risk of contributing to cancer causation and an exposure that definitely causes cancer?
MR. SLATER: Same objection.
You can answer.
A. Yes.
Q. What's the difference in your mind?
MR. SLATER: Same objection.
You can answer.
A. We are using the available data to determine whether it's probable or even likely that certain exposure could cause cancer versus another situation where we know perhaps a person has been treated with a chemotherapeutic drug that has carcinogenic side effects where you know on an

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individual basis that you know the chemotherapeutic drug caused perhaps a second cancer, a different cancer than the one the person was being treated for.
I don't know. Does that answer your question?
Q. I'm not sure.
A. So in this particular case, we don't know about the individual exposure and outcome. All we know about is that the valsartan drug contained a carcinogen. Whereas in the other case that you mentioned, I believe what you were saying is we know if we administer a certain cancer causing agent to a given person and that person gets cancer, then we know cause and effect in that individual.
Is that your question?
Q. I'm not sure that was my question, but I think what I heard you say is that in some instances, we can tell cause and effect with reasonable certainty and some instances, we cannot?
MR. SLATER: Objection.
You can answer.
A. I don't know what you mean by

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reasonable certainty.
Q. Well, expert opinions -- strike that.
Expert witnesses in civil litigation of this nature are supposed to provide scientific testimony to a reasonable degree of scientific certainty.
Is that your intention today?
A. Yes.
Q. So to a reasonable degree of scientific certainty, what I'm asking you is are there instances where we can definitively determine the cause of cancer and instances where we could not?
MR. SLATER: Objection.
You can answer.
A. Yes, there are instances where we can definitively determine the cause of cancer.
Q. So what I'm trying to understand, sir, is the opinion that you intend to offer in this case.
Did NDMA and NDEA in valsartan-containing medications increase the risk of cancer or do you intend to offer the opinion that small amounts of nitrosamines observed in the valsartan-containing medications definitively

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caused cancer?
MR. SLATER: Objection.
Multiple reasons.
You can answer, Dr. Hecht.
A. They increased the risk of cancer.
Q. Now, there are lots of risk factors for cancer; true?
A. Yes.
Q. Old age is a risk factor, correct?
A. Yes.
Q. People over the age of 50 are at an increased risk of cancer; true?
A. Correct.
Q. People over the age of 50 are at an increased risk of cancer regardless whether they take valsartan; true?
A. Yes.
Q. People over the age of 50 are at an increased risk of cancer regardless of whether they took valsartan containing small amounts of nitrosamines; true?
MR. SLATER: Objection.
You can answer.
A. Yes.
MR. SLATER: Dr. Hecht, one second.

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Just give a pause because he's going pretty quick and I need to have a little time to place my form objections to the questions and then I would expect I'll go ahead and say you could answer every time or virtually every time, but just give a little pause so I don't step on your answer.
Okay?
THE WITNESS: Okay.
Q. That's fair, Dr. Hecht. I probably should have told you at the beginning, that especially taking these depositions remotely, we have to be careful not all to speak at the same time because if you and I or Adam and I are speaking at the same time, the audio tends to go out and the court reporter can't take everything down. If you could try to pause before -- after I finish my question, give Adam a chance to interject if he needs to, that will make things go a lot more smoothly. My fault for not covering.
Okay?
A. Okay.
Q. So is a family history of cancer also a risk factor for cancer?
A. Yes.

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Q. Is tobacco use a risk factor for cancer?
A. Yes.
Q. Is alcohol use a risk factor for cancer?
A. Yes.
Q. Is obesity a risk factor for cancer?
A. Yes.
Q. What you are saying here today or what your opinion that you intend to offer in this case is is that increased nitrosamine intake is also a risk factor for cancer, you believe?
A. Yes.
Q. I assume we could also agree right off the bat, Dr. Hecht, that just because something is a risk factor doesn't mean that it caused cancer?
A. Correct.
Q. You can be 400 pounds, but that doesn't mean that's the reason why you develop lung cancer; true?
A. Correct.
Q. Do you also understand and can we agree that the question of whether a substance is capable of causing cancer is dependent on dose and

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duration of exposure?
A. Yes.
Q. And --
MR. SLATER: Belated objection.
It went a little quick, but you could continue.
Q. The reason I thought we could agree on that is you seemed to acknowledge that fact in the conclusion of your report on page 27 when you write that any increased risk would be commensurate with the impurity level, the dose and the period of use.
Is that right?
A. Yes.
Q. Are you familiar with the old adage that "The dose makes the poison"?
A. Yes.
Q. Do you agree with that statement?
A. Yes.
Q. All substances -- strike that.
Virtually all substances known to man have a capacity to be toxic at some level; true?
MR. SLATER: Objection.
You can answer.
A. All substances known to man? I don't

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know about that.
Q. Well, let me give you a for instance.
Water is a life-sustaining substance, correct?
A. Yes.
Q. However, water can be deadly when it's consumed to excess; true?
A. Yes.
Q. So there are -- you didn't want to agree with virtually all, but there are many substances that have the capacity to be harmful at some level; true?
A. Yes.
Q. And since there are many substances that have the capacity to be harmful at some level, looking at exposure levels, dose and duration would be a reasonable and necessary approach when evaluating cancer causation; agreed?
A. Yes.
Q. The question in this litigation to be answered is not whether nitrosamines can cause harm at any level.
Do you understand the question that we're interested in getting at is whether there's credible scientific evidence that the small

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amounts of NDMA that was contained in valsartan-containing medications can cause cancer in humans.
Can we agree on that?
MR. SLATER: Objection to the form of the question.
You can answer.
A. Yes.
Q. I guess a second question to be answered is whether small tiny amounts of NDEA found in valsartan-containing medications can cause cancer in humans, right?
MR. SLATER: Objection to the form of the question.
You can answer.
A. Yes.
Q. Since we can agree on the questions to be answered, I take it that what the reason that you're here is that you were retained by Mr. Slater and the lawyers and the plaintiff group to help analyze and provide answers to those two questions.
Is that accurate?
MR. SLATER: Objection.
You can answer.

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A. Yes.
Q. So in broad strokes, Dr. Hecht, tell me generally what work you did to answer those two questions.
MR. SLATER: Objection.
You can answer.
A. Well, I looked to the literature and all of the data regarding the contamination of valsartan with dimethylnitrosamine, dimethylnitrosamine. My conclusion was that it posed -- that it should not have been there, first of all, and it posed an unacceptable risk to people using these medications.
Q. Let me stop you. It sounds like you were finished anyway, Dr. Hecht. If my question was unclear, I apologize. I wasn't really interested in getting at all of your opinions right now.
My question was if you could just tell me in a general fashion what work you did to answer the questions or to form your opinions.
You told me that so far you looked up literature, correct?
A. Yes.
Q. You told me that you looked at some

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data on nitrosamine levels in valsartan products from some manufacturers, correct?
MR. SLATER: Objection.
Mischaracterization of the testimony.
You can answer.
A. Yes. I looked at what's in the literature and what's in the documents that I was given.
Q. Okay.
So again, I'm just looking for broad strokes in terms of what work you did to sit down and write this report that we marked as Exhibit 1.
You've told me looking at literature and looking at documents and I assume we're talking about company documents that were provided to you by Mr. Slater and his team, right?
A. Yes, in part. And also published literature like the EMA report.
Q. Okay.
A. Other publications in the open literature that have discussed this.
Q. Okay.
My apologies for interrupting you there briefly.
Other than looking at the literature

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and documents that were provided to you by Mr. Slater and his team, is there anything else you did to sit down and write the report that we marked as Exhibit 1?
MR. SLATER: Objection.
You can answer.
A. Anything else that I did? I, you know, depended on my experience and knowledge of the literature about nitrosamine carcinogenesis. So I depended on that knowledge, I drew on it to write the report.
Q. Sure.
Now, I understand -- and I'm going to get into your background in a little bit -- but I understand you drew upon and relied upon your background in reaching conclusions based on your review of the literature and review of the documents provided to you by Mr. Slater.
That's what you're telling me, correct?
A. Yes.
Q. Was there any other work that you actively did to prepare the report other than what we've described?
A. I'm not sure exactly what you mean by

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other -- I wrote the report based on the sources that I had.
(Whereupon, Exhibit 2 was marked for identification.)
Q. So let's -- let me ask you some questions about your background then.
I have attached as Exhibit 2 a copy of your CV, which contains a rather large bibliography.
Do you happen to have a copy of your CV with you, Dr. Hecht?
A. It's on my computer. I don't have --
MR. SLATER: It's also attached to the report, Doctor. Or it should be.
Q. Well, if you need to refer to it to answer my questions, feel free.
Okay?
A. Okay.
Q. But does the -- can you tell me whether the CV that we've marked as Exhibit 2 and which is attached to your report contains an accurate list of your professional qualifications?
A. Yes.
Q. Is it complete and up to date as far as you know?

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A. Yes.
Q. Is there anything that you'd like to add or remove from the CV?
A. No.
Q. Based on my review of your CV, it appears your formal education is in the field of chemistry; is that true?
A. Yes.
Q. You have a bachelor's degree in chemistry from Duke University; true?
A. Correct.
Q. And a PhD in organic chemistry that you obtained in 1968, correct?
A. Right.
Q. Did you have to write a thesis to obtain that PhD?
A. Yes.
Q. What was the subject matter of your thesis?
A. The thesis was divided into two parts. The first part had to do with transannular carbene reactions. I'm not sure if you want me to go into detail about that.
Q. That's all right.
A. The second part dealt with the

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photolysis of phenoxy compounds.
Q. Sounds rivetting.
A. Yes.
Q. That was a poor attempt at humor.
A. Yes, I know.
Q. Did your thesis touch on nitrosamines?
A. No.
Q. May I ask your age, sir?
A. Seventy-eight.
Q. You mentioned earlier when I asked you your occupation, you indicated you're a professor, so currently you're in academia, right?
A. Correct.
Q. Are you an employee of the University of Minnesota?
A. Yes.
Q. And so you draw a salary from the university; is that right?
A. Yes.
Q. According to the CV, you're a professor in the Department of Laboratory Medicine and Pathology.
A. Correct.
Q. To be clear, though, you were not a

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pathologist; agreed?
A. Yes.
Q. Are you a medical doctor?
A. No.
Q. Since you're not a medical doctor, I take it you do not diagnose cancer in patients, correct?
A. Correct.
Q. Have you ever diagnosed a patient with esophageal cancer?
A. No.
Q. Have you ever diagnosed a patient with colorectal cancer?
A. No.
MR. TRISCHLER: I'm going to mark as Exhibit 3 a document that's entitled "Plaintiffs' Disclosure of Cancer Types."
To our technician, this is one you can put up on the screen for me.
(Whereupon, Exhibit 3 was marked for identification.)
Q. Are you able to see that document, Dr. Hecht?
A. Maybe you could make it a little larger.

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Q. I can't, but there's --
THE VIDEOGRAPHER: Is there a specific section you'd like me to blow up?
MR. TRISCHLER: Just the text in the middle.
THE WITNESS: Okay.
Q. Have you ever seen this document before, sir?
A. Let me just read it first.
Okay?
Q. Sure.
(Witness reviews document)
A. No, I've not.
Q. I'll represent to you that this is a disclosure that was filed by the plaintiffs in this litigation. It's a list of cancer types that have been placed at issue in this litigation.
Okay?
A. Okay.
Q. Take a look.
Do you see there are 13 cancer types listed? Do you see that?
A. Yes.
Q. Have you ever diagnosed any of these cancer types in any patient?

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A. No.
Q. Have you ever treated a cancer patient?
A. No.
Q. Going back to your role at the University of Minnesota, are you actively teaching at the moment?
A. No.
Q. Are you going to be teaching any courses in the 2021/2022 academic year?
A. No.
Q. When was the last time you taught a graduate level course?
A. That's about ten years ago.
Q. What was the course you taught some ten years ago?
A. Chemical carcinogenesis.
Q. Did you use a textbook for that course?
A. No. We used the current literature.
Q. Who were you teaching that graduate level course to? Was it medical students at the medical school or was it in some other environment?
A. It was a mixture that -- there

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weren't medical students.
Q. Was it a graduate level course in some --
A. In carcinogenesis. The students came from different programs in the university, but there weren't medical students. There were graduate students in medicinal chemistry or from the St. Paul campus on nutrition.
Q. Thank you.
I'm trying to get an understanding was it a class that was offered by the Department of Chemistry, the Department of Biology. Help me understand that, if you can.
A. No, it was a graduate course in -- actually, I've forgotten exactly which division it was listed in. I don't recall whether it was medicinal chemistry or whether it was in the C fans, the food and nutrition. I'm sorry. I don't remember.
Q. That's okay. It's been ten years -- I understand it's been ten years since you offered the course, correct, or taught the course?
A. Yes.
Q. Has it been ten years since you've been in the classroom at Minnesota?

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A. Yes.
Q. Have you ever taught an undergraduate course at the University of Minnesota?
A. No.
Q. Are you a full-time employee at this point or have you slowed down?
A. No, I'm a full-time employee.
MR. TRISCHLER: You can remove that exhibit, sir.
Thank you.
Q. Are you actively involved in any research projects at the moment?
A. Yes, I am.
Q. I think in your report that's marked as Exhibit 1 to this deposition you indicate at the bottom of page two that you are the principal investigator on three R01 grants --
A. RO1.
Q. Correct?
A. Yes.
Q. By the way, the Masonic Cancer Center is designated as a comprehensive cancer center, correct?
A. Correct.
Q. I think that's a designation given by

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the National Cancer Institute?
A. Correct.
Q. And Masonic would be one of over 50 hospital systems over the country that have been so designated, right?
A. About 50, yeah.
Q. The National Cancer Institute has also designated seven laboratory centers across the country that do cutting edge cancer-related research, correct?
A. Right. Those are laboratory centers. Comprehensive center includes not only laboratory research, but also treatment.
Q. But Masonic is not one of the seven laboratory cancer centers designated --
A. It's a comprehensive center, which includes laboratory work.
Q. Going back then to the RO1 grants, these are projects that are funded by federal grants; is that right?
A. Yes.
Q. To whom were the three RO1 grants that you reference in your report issued?
A. Well, I'm the principal investigator, but the grants are actually issued to the

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University of Minnesota.
Q. Can you describe the subject of those three current grants?
A. Yes. One of them involves the mechanisms and prevention of tobacco-induced cancer caused by a group of carcinogens in tobacco products that we discovered and have worked on for many years called tobacco specific nitrosamines.
The second grant --
Q. I'm sorry.
Would those be NNN and NNK?
A. Correct. Do you want me to go on or do you want me to --
Q. Yes, please.
A. The second grant has to do with the carcinogens and toxicants that are possibly omitted from e-cigarettes that are present in e-cigarette paper and could be taken up by people who use these products.
The third one is a clinical trial of watercress for -- to enhance the detoxification of environmental toxicants and carcinogens.
Those are the three RO1 grants. I'm also the PI of a program project grant on the ethnic differences in cancer risk due to cigarette

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smoking.
Q. Okay.
Thank you for the descriptions.
The third one -- the third RO1 grant you mentioned, I'm not sure if I didn't hear you or didn't understand you. You said it was a clinical trial involving what?
A. Watercress.
Q. Forgive my ignorance.
What's watercress?
A. It's a plant.
Q. Okay.
A. It's a common food that people use in salads. Watercress.
Q. Is it carcinogenic?
A. No. Not at all.
Q. What does the clinical trial involve?
A. So we found over the years in other studies that we've done that a compound that's present in watercress called PEITC -- or phenethyl isothiocyanate -- can prevent lung cancer in rats and mice treated with tobacco carcinogens. Based on that work, we performed a clinical trial with our colleagues here at the University of Minnesota to determine whether PEITC would have a similar

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effect in cigarette smokers as it did in laboratory animals, whether it could therefore be used as a chemo-preventative agent in people who couldn't stop smoking because they're addicted to nicotine. This compound was able to prevent cancer in animals treated with tobacco specific nitrosamines, as I mentioned.
So in this clinical trial, we found that PEITC did, in fact, decrease the metabolic activation of NNK in smokers, which was the hypothesized result. But the decrease was, while significant, was quite small.
However, in the same trial, we found that certain people who took the PEITC had a great increase in their ability to detoxify environmental toxicants like benzene. This formed the basis for the watercress study because watercress is a great source of PEITC. Just a salad-sized portion of watercress will, when you eat it, when you chew it, will release 20 to 30 milligrams of PEITC, which was similar to the dose of the pure compound we had used in the study that I described.
So that's what gave rise to the watercress trial.

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Q. All right. I understand what you're doing now in that study. I appreciate the details.
So you've now told me about your current RO1 grants and your --
A. Grant project.
Q. -- correct.
A. Yes.
Q. Do any of your current RO1 grants or the program project grant deal specifically with NDMA or NDEA?
A. The one on tobacco specific nitrosamines, while the specific names aren't dealing specifically with NDMA, it's closely related to NNK in terms of its mechanistic properties.
So the answer -- the short answer to your question is no, but the longer answer is that yes, it's closely related.
Q. Well, I understand that NDMA and NNN or NNK might be chemically related, but my question was are these grants dealing specifically with NDMA or NDEA grant research?
A. Not specifically. Not in the specific names.

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Q. Have you ever been involved in any federally-funded research products dealing directly with the carcinogenicity of NDMA?
A. Yes.
Q. Can you tell me about those, please?
A. Well, when I was still at the American Health Foundation, we did studies that compared the carcinogenicity and metabolism of NDMA and NNK. We did this because NNK was a relatively -- a relatively new carcinogen that hadn't been explored with a regard to its carcinogenic properties and mechanisms of action, whereas NDMA has been known as a carcinogen since 1956.
So since NDMA was such a well-established carcinogen, we thought it would be important to compare some of the properties of NNK and NDMA, so we did do those studies.
Q. I think that was back in the 1980s, you said?
A. Yes.
Q. It was a comparative analysis of the potency of NDMA to NNK?
A. Yes.
Q. You published the results of those --

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of that study, correct?
A. Yes.
Q. And I think it was an animal study involving rats; is that right?
A. Yes.
Q. Have you ever been involved in your career in any federally-funded research projects involving the carcinogenicity of NDEA?
A. Not specifically.
Q. Have you ever been involved in any research projects that focused on the human body's metabolism of NDEA?
A. Human NDMA? No, not directly.
Q. Have you ever been involved in any research projects that focused on the human body's metabolism of NDEA?
A. Not directly, no.
Q. Have you ever been involved in any research projects devoted to analyzing the mechanisms of action of cancer induction from NDMA?
A. Yes.
Q. Would that be the same study that you told me about before, the rat comparison to NNK?
A. That was one, yes.

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Q. Have you ever been involved in any research projects devoted to analyzing the mechanism of action of cancer induction from NDEA?
A. Not directly.
Q. Since you don't have a medical degree, I take it you're not Board Certified in oncology, radiology or any other medical discipline, right?
A. Correct.
Q. Are you an expert in the field of epidemiology?
A. I have worked with epidemiologists throughout my career, yes.
Q. I have, too. Does that make me an expert in epidemiology?
MR. SLATER: Objection to the form.
You can answer.
A. I don't know. I don't know if you're an expert in epidemiology.
Q. Do you hold yourself out as an expert in the field of epidemiology?
A. That depends on your definition of the word "expert."
Q. Do you agree that epidemiology is the study of the distribution and determinants of a

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disease in a population?
A. Yes.
Q. Do you have a degree in epidemiology?
A. No.
Q. Are you Board Certified in the field of epidemiology?
A. No.
Q. Are you a pharmacoepidemiologist?
A. Pardon me?
Q. Are you a pharmacoepidemiologist?
A. No.
Q. Do you have a degree in pharmacology?
A. No.
Q. Do you agree that pharmacology is the study of effects of drugs on a population?
A. Yes.
Q. Have you ever been trained or employed as a clinical pharmacologist?
A. No.
Q. Are you a molecular biologist?
A. No.
Q. On your CV and also in response to one of my earlier questions, you mentioned you were affiliated for a time with the American Health Foundation.

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Is that right?
A. I worked there for 23 years.
Q. That was before you moved to the University of Minnesota, right?
A. Correct.
Q. Why did you leave the American Health Foundation?
A. I was concerned about the future of the foundation and also I had a very nice offer from the University of Minnesota.
Q. Nice offer from who?
A. The University of Minnesota.
Q. I'm sorry. Sometimes I don't hear great and sometimes with the computer your voice trails off a little bit, Doctor. If I ask you to repeat yourself, it's just because I couldn't hear the answer.
Okay?
A. Okay. Sure.
The offer was from the University of Minnesota. The cancer center in particular.
Q. Understood.
When you were at the American Health Foundation, according to your CV, you held the title of Director of Research for over nine years;

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is that right?
A. Yes.
Q. Were you in charge of all the foundation's research activities during that nine-year period?
A. That depends what you mean by "in charge of." I was responsible for overseeing and coordinating the research. It was up to the individual investigators to get the research funded. My role was to bring people together to look for opportunities for interdisciplinary collaboration and also to write the cancer center grant application from the foundation to the National Cancer Institute.
Q. The vast majority of the funding of the American Health Foundation came from federal grants and contracts awarded through NCI, correct?
A. Correct.
Q. So you would have to write the grant applications to outline the scientific basis for the research that you wanted to conduct so that you could get those federal funds into the facility to do that work?
A. Yes. That's true, but each individual principal investigator was responsible

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for -- also responsible for funding their own research through grants and contracts mostly from the National Cancer Institute.
Q. To whom did you report in your role as Director of Research when you were at the American Health Foundation?
A. To Ernst Wynder, president and founder of the foundation.
Q. At some point in time, the American Health Foundation changed its name to the Institute for Cancer Prevention, right?
A. That was just The Institute. So the foundation included two branches. There was a branch in New York City, which focused on epidemiology. That was Dr. Wynder's specialty. You may be aware that he was the first to -- in this country -- to establish the relationship between smoking and lung cancer.
Then there was The Institute, which was in Westchester County, which was the basic research, the laboratory research part of the foundation. My role was Director of Research of the laboratory part of the foundation.
Q. I understand.
The foundation, though, changed its

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name to the Institute for Cancer Prevention, right?
A. No. The foundation never changed its name. It's the Naylor Dana Institute, which is the basic research institute. It changed its name to Institute for Cancer Prevention. That was after I left.
Q. Where is the health foundation today?
A. It went out of business in the late 90s.
Q. It's out of business just as the IFC is out of business, right?
A. Yes.
Q. They filed for bankruptcy, right?
A. I believe. Something like that. I don't really know the details.
Q. Several of the leaders of that organization were indicted on federal charges, right?
A. There were some problems, yes. This was all after I left. Well after I left.
Q. The leaders of the American Health Foundation and IFCP were indicted on charges of improperly diverting and misusing federal funds for cancer research, right?

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A. Something like that, yes.
Q. Several of the members of the management group, including the CFO, pled guilty to those charges, right?
A. I guess so.
Q. Were any charges ever brought against you?
A. No.
Q. Were you ever interviewed or investigated by the FBI in connection with AHF and IFCP's misuse of federal funds?
A. No.
Q. In addition to the criminal matters, there were also a lot of civil charges that were brought by the United States Department of Justice against your old employer and its employees, right?
A. I really don't know anything about that.
Q. Were any charges -- civil charges -- brought against you from your work at --
A. No.
Q. -- AHF?
A. No.
Q. Isn't it true that many of the

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allegations that were brought by the federal government involving misuse of funds at IFCP and AHF predate your departure from the organization?
A. I really don't know.
Q. You don't remember hearing anything about any of that while you were there?
A. No.
Q. You said earlier that you were concerned about the future of the organization, which is one of the reasons why you left.
A. Yes.
Q. Did your concern have something to do with the federal charges and federal investigations that were going on?
A. Not at all.
Q. Why were you concerned about the future of the organization when you were there?
A. Ernst Wynder's management style about, you know, the allocation of resources within the institute. It had nothing to do with any of the things you're talking about.
Q. The things I'm talking about actually happened.
You know that, right?
MR. SLATER: Objection.

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Is this an argument now that you'd like to start with Dr. Hecht or do you have another question?
MR. TRISCHLER: I thought I did ask a question, Adam.
MR. SLATER: I took it as argumentative and I object to it.
You can answer, but I'm sure he's going to -- Mr. Trischler will start asking direct questions instead of what just happened.
A. What was the question again?
Q. There were federal investigations, federal indictments and federal charges of fraud against AHF, IFCP and its employees for misuse of federal funds.
You are aware of that; true?
A. I heard about it.
Q. And at the time that you were Director of Research, isn't it true that AHF settled a federal lawsuit by paying the government millions of dollars to replace and reimburse the government for misuse of federal grant monies?
A. I don't know. I don't think that happened when I was there. It may have. I don't

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know. I honestly don't know.
Q. Were you ever deposed in connection with any of those lawsuits?
A. No.
Q. Did you ever given sworn testimony in connection with any of those lawsuits?
A. No.
Q. Was the scrutiny from the federal authorities and investigators anything that led to your departure from that company and your decision to head to the University of Minnesota?
A. No, not at all.
Q. In your report that I have marked as Exhibit 1, you indicated that you've been involved in the -- in research relating to nitrosamine since 1973.
A. Correct.
Q. That's true?
A. Yes.
Q. How many different nitrosamines have been identified by the scientific community?
A. How many have been identified?
Q. Yes, sir.
A. Do you mean in connection with cancer or --

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Q. No.
A. -- just in general? I mean, you know, there's an infinite number of possible nitrosamines that can be synthesized and identified. The actual number that have actually been identified by chemists, it's probably in the hundreds. I don't really know that number.
Q. Okay.
A. They're not all -- wouldn't all be with respect to cancer research. I mean nitrosamines have been known as a class -- chemical class long before they were known to be carcinogenic.
Q. I appreciate all that information and I understand that there may be nitrosamines that can be synthesized that have yet to be identified. I was just asking if you know generally from your involvement in this field how many have been identified both as carcinogenic and noncarcinogenic.
What you told me is that the number is in the hundreds, right?
A. Yeah. As carcinogenic?
Q. No. That wasn't my question.
A. Okay. What's your question?

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Q. Total number of nitrosamines that have been identified.
A. Independent of any biological activity?
Q. Yes.
A. In all the chemical literature?
Q. Yes.
A. I'm guessing between 100 and 200.
Q. I've seen research suggesting there's been as many as 300 nitrosamines identified. Would you dispute that?
A. That's possible, sure. Nitrosamines or nitroso compounds?
Q. Nitrosamines.
A. You're sure of that?
Q. So if we just use the number 300, while the scientific community has identified around 300 different nitrosamines, is it true that most of your research has focused on nitrosamines found in tobacco products?
A. Yes.
Q. For instance, you've told us here today that you continue to work on and do important research on tobacco-related nitrosamines like NNK and NNN?

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A. Yes.
Q. Your research was fundamentally important in identifying those nitrosamines as carcinogenic, correct?
A. Yes.
Q. Is NNK listed as a Class 1 carcinogen?
A. NNK and NNN are together considered Class 1 by IARC. They're listed together because they always occur together.
Q. While most of your work and research is focused on nitrosamines contained in tobacco products, is it fair to say that you've not researched all the 300 plus nitrosamines recognized by the scientific community?
A. Not all of them, no.
Q. Prior to your retention in this case, had you ever published any research dealing specifically with the carcinogenicity of NDEA in humans?
A. I think you asked me that before. No.
Q. I asked you before whether you'd done any research. This question is whether you published --

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A. No, not NDEA.
Q. Your work, your published research with respect to NDEA related to a comparative evaluation of the toxicity of NDEA to NNK, correct?
A. Correct. That was NDMA.
Q. If I misspoke, I apologize. Yes. In that comparative analysis --
A. Right.
Q. -- toxicity was an animal study done in rats, right?
A. Correct.
Q. Have you ever in the course of your career prior to your retention in this case published any research dealing with the carcinogenicity of NDMA in humans?
A. No.
Q. Prior to your retention in this case, had you ever published any research on human DNA repair capacity when exposed to NDMA or NDEA?
A. No.
Q. Prior to your retention in this case, have you ever published any peer-reviewed research dealing directly with the level of the reactivity

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stability and DNA binding of NDMA or NDEA when exposed to -- as a result of human exposure to those chemicals?
A. No.
Q. Prior to this case, have you ever studied and published on the efficiency of human metabolic enzymes in metabolizing and eliminating NDMA or NDEA?
MR. SLATER: Objection.
You can answer.
A. No.
Q. Did you answer, sir? If you did, I didn't hear.
A. The answer is no.
Q. Are you a pharmacokineticist?
A. No.
Q. Do you recognize pharmacokinetics as the discipline that's involved in studying the absorption, delivery, metabolism and elimination of substances from the body?
A. Yes.
Q. You've never been trained in that discipline, correct?
MR. SLATER: Objection.
A. Correct.

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Q. You've never published any research on the pharmacokinetics of NDMA or NDEA; is that true?
A. Yes.
Q. The CV that you provided to us which we marked as Exhibit 2 lists some major contributions to science that begin on page six. It's actually under the title "Selected Contributions to Science."
Are you familiar with that --
A. Yes.
Q. -- in your CV?
A. Yes.
Q. The first one that you list there is basically the study of tobacco-specific nitrosamines and the identification of NNN and NNK, which we talked about, correct?
A. Yes.
Q. Then you then list the -- number two as being the application of tobacco carcinogen and toxic and biomarkers in clinical and epidemiological studies, correct?
A. Correct.
Q. The third thing you list under your significant contributions to science is metabolism

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and DNA adducts -- adducts, A-D-D-U-C-T-S, for the court reporter -- of PAH and aldehydes.
Did I pronounce that correctly?
A. Yes.
Q. What is PAH and aldehydes? What are they?
A. Polycyclic aromatic hydrocarbons. Those are carcinogens present in the environment and in tobacco smoke that form as a result of incomplete combustion of organic matter. The best known of which is benzoapyrene.
Aldehydes are a class of chemical compounds. The best known are formaldehyde and acid aldehyde and acrolein that are formed in human metabolism of alcohol and they're also humans are exposed through the general environment and tobacco smoke, as well as endogenous roots.
Q. Okay.
Then the fourth of five things that you list under your contributions to science is chemo prevention of cancer and that's -- that involves studying things that can help prevent the carcinogenic effect of exposures, correct?
A. Yes.
Q. Like the RO1 study involving the

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salad we talked about?
A. Watercress, yes.
Q. Learn something new every day. I never knew what watercress was.
A. Now you know.
Q. Number five is expertise in tobacco carcinogenesis, correct?
A. Yes.
Q. In going through your CV and listing, you know, what your major scientific contributions have been during your long career, you don't mention anything specifically related to NDEA, true?
A. Correct.
Q. You don't mention anything specifically related to NDMA, correct?
A. Correct.
Q. Do you hold yourself out as an expert in toxicology?
A. No. I'm not a toxicologist.
Q. Are you a member of the Society of Toxicology?
A. No. I don't think I paid my dues. I was a member, but I'm not now.
MR. TRISCHLER: I'm not sure what

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that noise is.
Can everyone mute their line, please?
MR. SLATER: Someone is certainty off mute.
THE VIDEOGRAPHER: I just muted them for you guys.
MR. TRISCHLER: Sorry about that, Doctor.
Q. Prior to your retention in this case, did you ever conduct a toxicological evaluation of human health risks from exposure to NDMA?
A. No.
Q. Prior to your retention in this case, had you ever conducted a toxicological evaluation of human health risk from exposure to NDEA?
A. No, but I'm not sure exactly what you mean by toxicological evaluation. I mean, I've served on committees -- I do serve on a committee presently looking at nitrosamines and food and I've been on an FDA panel which talked about nitrosamine contamination of the drugs, so I'm not sure exactly what you mean by the question.
Q. Let me see if I could clear it up then.
Have you ever published in the

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peer-reviewed scientific literature any data that would provide a toxicological assessment of human health risk from exposure to NDMA?
A. Well, we published work that could contribute to that. As far as an overall toxicological evaluation, no.
Q. Have you ever published an overall toxicological evaluation of NDEA?
A. No.
Q. You list in your bibliography about 618 entries that you have been responsible for.
Do you recall that?
A. Yes.
Q. I know that one dealt specifically with NDMA because we've already talked a little bit about it. That would be the comparative study between NDMA and NNK, right?
A. Yes.
MR. TRISCHLER: Why don't we just go ahead and have that -- since we've been referring to it -- that paper marked. I think we'll mark it Exhibit 4 we're up to.
(Whereupon, Exhibit 4 was marked for identification.)
Q. It's entitled, for the record,

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"Comparative Tumorigenicity of DNA Methylation in F344 Rats by Methylnitrosamino Butanone and Nitrosodimethylamine."
How did I do in the pronunciations?
A. Pretty bad.
Q. Surprising.
Do you have that paper in front of you or do you need it? If not, I could have it put up on the screen?
A. I don't have it in front of me.
MR. TRISCHLER: Bill, can you put it up?
THE VIDEOGRAPHER: Sure.
What is the name of the file? I don't see one that started with what you had announced.
MR. TRISCHLER: I think the file would be Comparative Tumorigenicity --
THE VIDEOGRAPHER: I'm not seeing -- I'm going to scroll through. I'm going to see if it's maybe labeled something else.
Yes, got it. One moment.
Q. So I put up as Exhibit 4 at least the first page of your paper that we've been talking about, Dr. Hecht.

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To go through this efficiently, I'll just ask questions and if you need to review or consult any part of your paper to answer them, please let me know that and we can take as much time as you need to read the document or to review a section of it.
Okay?
A. Okay.
Q. In this paper, as we've already talked about, the purpose of it was to compare the toxicity and potency of NNK to NDMA, right?
A. The carcinogenicity, yes. Not necessarily the toxicity.
Q. Okay. Understood.
As I understand it, a group of 30 rats was given IV doses of NNK for 20 weeks; is that right?
A. IV?
Q. Yes, that's what I said.
A. Sub Q I thought it was.
Q. Okay. There's a section marked "Bioassay" on the first page there. Can you blow that up for the doctor? Maybe I misread it, but --
A. SC. Subq. Subcutaneous injection,

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not IV.
Q. Okay.
So we had a group of 30 rats that were given subcutaneous injection doses of NNK for 20 weeks, right?
A. Yes.
Q. Another group of 30 that were given NNK for the same period of time?
A. Correct.
Q. By the way, 20 weeks is about 20% of the life expectancy of a rat, right?
A. Twenty weeks, something like that.
MR. SLATER: Before we continue, can you please put that document in the folder so it would be accessible to everybody?
MR. TRISCHLER: Sure.
THE VIDEOGRAPHER: It should be in there. Are you not seeing it? I would just suggest --
MR. SLATER: Not there.
MR. TRISCHLER: All the exhibits should be placed in the chat or in a folder for everyone's --
THE VIDEOGRAPHER: Just try to refresh the page.

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MR. SLATER: It's in there now.
THE VIDEOGRAPHER: Great.
MR. SLATER: Sorry about that.
MR. TRISCHLER: That's all right.
BY MR. TRISCHLER:
Q. So dosing a rat for about 20 weeks or 20% of its life expectancy would be the equivalent of dosing a human for about 15 years, correct?
A. Yeah.
Q. And you understand that when we talk about this case for just a moment, you understand that there's no plaintiff in this litigation who ingested valsartan-containing medications containing nitrosamines for 15 years, right?
A. Correct.
Q. And the total dose that was given to these rats in your study was listed as 0.33 mmol/kilogram.
Is that right?
A. Yes.
Q. Can you equate that to a human dose for a 150-pound individual?
A. You want me to do that now?
Q. Are you able to?
A. I'm able to, yeah, but I don't know

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if I could do it in my head. So 0.3 millimoles per kilogram, so a 150-pound person is about 70 kilograms. 0.3 millimoles per 70 kilograms would be -- I don't know. I can't do it in my head. I'm sorry.
Q. That's fair. I couldn't do it either.
I'll represent to you I did run this --
A. It's significantly higher than the human dose, if that's what you're getting to. We don't have to waste time going through -- I mean, the purpose of this experiment was to compare NNK and DMN -- NDMA.
Q. Understood.
A. The dose -- the dose is far higher than a human dose. If you want to get to human dose, you have to look at the Peto study.
Q. We'll get there.
What we can agree upon is that in this particular study that the dose administered to rats was on order of magnitude greater than the nitrosamine levels seen in valsartan-containing medications, correct?
A. Yes, absolutely.

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Q. And there is a formula for converting these doses to a human equivalent dose, correct?
A. Yes.
Q. I think we can agree that formula is not easy to do in one's head, but I've done the math and I'll represent to you that the human equivalent dose in this study would equate to about 336 million nanograms.
Does that sound about right?
A. I'll take your word for it. But I mean this study was not designed to look at human doses at all.
Q. It wasn't designed to look --
A. It was designed to compare NNK and NDMA carcinogenicity and metabolism using the doses of NNK that we knew induced a certain percentage of lung tumors.
Q. This study that we marked as Exhibit 4 was not designed to look at issues of human carcinogenicity of NDMA, correct?
A. That's a very broad statement. It wasn't designed to replicate the human dose of NDMA. Not at all.
Q. Okay.
The point is that the animals in your

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study were administered nitrosamines in far greater quantities and over a greater period of their life span than any plaintiff in this litigation.
Can we agree on that?
A. That's the point you're making, yes.
Q. And is the point I'm making accurate?
A. Yes.
Q. After a long period of exposure at doses far higher than what's contained in any of the valsartan-containing medications, what your study showed was a development of tumors in six of the 30 rats that were administered these high, high doses of NDMA, right?
A. Yes.
MR. SLATER: Objection.
Lack of foundation and multiple other objections.
You can answer.
A. Yes.
Q. In the conclusion of your study was that NNK is more potent than NDMA?
A. That was the conclusion.
Q. And we know today that NNK and NNN are Class 1 known carcinogens, right?

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A. Yes.
Q. NDMA is not?
A. Correct. It's 2A.
THE VIDEOGRAPHER: Counsel, I just want to let you know I have about ten minutes left on this media before I need to do a quick break to change.
MR. SLATER: Why is that? Aren't you just recording with the Zoom?
THE VIDEOGRAPHER: We run an hour and a half. It's a Veritext standard.
MR. SLATER: Well, is it technological issue or is it just a Veritext standard?
THE VIDEOGRAPHER: Well, you know, it necessitates the issue that if we go two hours and it crashes, we lose two hours as opposed --
MR. SLATER: Okay. I got it. It's a Veritext issue. Thank you.
You can continue.
MR. TRISCHLER: Adam, would you want to stop now or go --
MR. SLATER: I've never heard of any such thing. I've been in 100 depositions in

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the last year and I haven't heard anyone say we need to stop because of the media cut off. There's a first for everything. We want to use as much time as we can and keep going.
MR. TRISCHLER: Bill, you could take down Exhibit 4.
BY MR. TRISCHLER:
Q. So before we started talking specifically about your paper that we marked as Exhibit 4, Dr. Hecht, I was asking about your bibliography.
Those 618 entries that are on it, do any of them deal specifically with the carcinogenicity of NDEA?
A. No.
Q. Other than the comparative paper that we marked as Exhibit 4, do any of those 618 papers that you list on your bibliography deal with the carcinogenicity of NDMA in any way?
A. No.
Q. You also list on your -- as part of your CV that we marked as Exhibit 2 some 280 chapters, articles and what's called other papers.
Are you familiar with that section of your CV, sir?

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A. Yes.
Q. Do any of those 280 chapters, articles or other papers deal specifically with the carcinogenicity of NDMA?
A. Yes.
Q. Can you tell me which ones?
A. No. I've written a number of chapters for books dealing with the metabolic activation or metabolism usually of nitrosamines and NDMA metabolism is kind of the classic example. So in a number of those chapters, NDMA will have been used as an example of the metabolic activation process by which nitrosamines are metabolized and bind to DNA leading to miscoding and activation of ANCA genes and cancer.
Q. You've told me --
A. That's covered in a number of those book chapters.
Q. You told me that you have your report in front of you in a hard copy form and I know the bibliography is part of the report.
What I'd ask you to do is go to the section marked "Chapters, Invited Articles, Books and Other Papers" and look at it and identify for me a few of the places that I can go to read what

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you've written about NDMA.
A. Okay. Well, I don't have the hard copy of the bibliography in front of me, so I'll have to pull it up on my computer. Then I can go through and then I can tell you. That'll take a few minutes.
MR. TRISCHLER: All right. We need to take a break for the videographer, so let's take a break. If you don't mind looking at that --
MR. SLATER: No, Clem. We're not going to do that during the break. I don't want to him doing work that should be on the record during a break.
MR. TRISCHLER: Well, we could do it when we come back then, Adam --
MR. SLATER: Yeah, I just want him to be able to take a break, stretch his legs and all.
MR. TRISCHLER: That's fine. Whatever you want to do. Let's take a break, we'll get the medium up and running and when you're ready to come back, we will pick up with this.
MR. SLATER: Let's take no more than

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ten minutes and come back.
THE VIDEOGRAPHER: The time is 10:37. We're going off the video record.
This ends media one.
(Recess taken)
THE VIDEOGRAPHER: The time is now 10:49.
This begins media two.
You may proceed.
Q. Welcome back, Dr. Hecht.
Before we took a break, we were talking about the section of your bibliography that's part of Exhibit 2 entitled "Chapters, Invited Articles, Books and Other Papers."
Do you remember that?
A. Yes.
Q. Have you been able to find that section of your bibliography on your desktop there?
A. Yes.
Q. I had asked if you would be kind enough to peruse that section and just identify for me a couple of the publications that you were a part of that discuss NDMA.
A. Right. I couldn't quite do that, so

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I have to -- that'll take some more time.
Q. You could do it now.
A. Okay.
(Witness reviews document)
Q. Dr. Hecht, may I make a suggestion while you're doing this?
A. Yes.
Q. If you have located three or four that are responsive, that's all I need. I'm not looking for you to tell me every single one. Just a few.
A. Okay. So the question is whether they specifically have dimethylnitrosamine as opposed to nitrosamines in general, correct?
Q. Correct.
A. That's the problem I'm having because I don't remember whether I specifically talked about dimethylnitrosamine, but -- so there's one paper in Environmental and Occupational Medicine, Third Edition, 1998. It's a chapter on N-nitrosamines.
Q. What number on the bibliography, sir?
A. It's 149 under the "Chapters" section. One forty-nine. That would be an example.

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Q. I'll accept that. You don't need to look at any further.
A. All right.
Q. So let me ask sort of the same question, but this time related to NDEA.
Do any of the chapters, invited articles, books or other papers listed in your CV that we've marked as Exhibit 2 specifically deal with or discuss the carcinogenicity after NDEA?
A. No, I don't believe so.
Q. Are you familiar with the term "threshold dose" as used in the field of toxicology?
A. Yes.
Q. What do you understand that term to mean, sir?
A. A dose below which there would be no effect.
Q. By no effect, you mean no toxicity or harm is --
A. Right. Whatever the end point is.
Q. In your career, have you ever done any original research to evaluate or establish a threshold dose for NDMA in humans?
A. No.

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Q. Have you ever done any research to evaluate a threshold dose for NDEA in humans?
A. No.
Q. Let me ask a little bit about valsartan if I can.
Do you understand that valsartan falls into a class of drugs known as angiotensin receptor blockers or ARBs?
A. Yes.
Q. Do you understand that ARBs are used in the treatment and management of hypertension?
A. Yes.
Q. Hypertension and heart disease are the number one cause of death of adults in America; true?
A. Yes.
Q. Do you agree that valsartan-containing medications have proven to be effective in the treatment and management of this deadly condition?
A. Yes.
Q. Do you agree that valsartan-containing medications are an important tool for clinicians to manage and treat this deadly disease?

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MR. SLATER: Objection.
You can answer.
A. Yes.
Q. Do you intend to offer any opinions asserting that valsartan is not effective in treating hypertension?
A. No.
Q. Do you intend to offer any opinion that the small amounts of nitrosamine impurities found in certain valsartan-containing medications compromised, limited or reduced the medication's effectiveness in controlling blood pressure?
MR. SLATER: Objection to the form.
A. No.
Q. You personally do not treat heart disease, correct?
A. Correct.
Q. You're not an expert in the diagnosis, treatment, management of this condition; fair to say?
A. Correct.
Q. Have you ever been prescribed valsartan-containing medications?
MR. SLATER: Objection.
Don't answer the question.

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I don't think it's appropriate to ask an expert, whatever the question is about, about their own personal health history.
MR. TRISCHLER: Only reason I ask, Adam, is if he could be a potential plaintiff, it goes to bias. If he's used these medications, it's certainly relevant.
MR. SLATER: That's why you're asking the question? To find out if there's a bias issue?
MR. TRISCHLER: To find out if he's used the medications that he's claiming --
MR. SLATER: I'll let Dr. Hecht --
MR. TRISCHLER: If he has a potential claim, I think it's relevant.
MR. SLATER: All right.
I'll allow Dr. Hecht to answer one question of whether he's used valsartan.
A. No, I haven't.
Q. Can we agree that hypertension is a major health problem?
A. Yes.
Q. Are you aware that the CDC is estimating that 45% of adult Americans suffer from hypertension?

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MR. SLATER: Objection to all these statistical proffers.
You can answer.
A. I didn't know that number offhand, but, you know, I'll take your word for it.
Q. Does hypertension cause cancer?
A. No.
Q. Is hypertension is risk factor for cancer?
A. No.
Q. As someone who is --
A. It's not a known risk factor.
Q. Are you aware of whether or not there are peer reviewed -- strike that.
Are you aware as to whether or not there is peer-reviewed literature that's been published in the medical community noting a statistically significant association between hypertension and cancer?
A. I'm not aware of it. I may have seen it. I can't think of it right now.
Q. As part of your work in this case, did you do a literature search to determine whether or not there was peer-reviewed literature discussing, noting or observing a statistically

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significant observation between hypertension and cancer?
A. No, I did not.
Q. Have you ever done such a literature search?
A. Not recently.
Q. Can we agree that cancer causation is multifactorial?
A. Yes.
Q. I think in going through your CV one of the things I observed in connection with your work as a professor or research that you've done, much of it is focused on cancer prevention, correct?
A. Correct.
Q. As someone who is focused on cancer prevention, one of the things that we've been taught is that good health and good diet can go a long way to reducing an individual's risk factor for developing cancer, correct?
A. Yes.
Q. While we know, based on the research that's been done in the past few decades, there are things we could do to reduce our risk factor to cancer, we still don't know what causes cancer.

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Would you agree?
A. Yes.
Q. While there's certainly no guarantees, what we believe is that a good diet, exercise and good health can go a long way in reducing an individual's risk; true?
A. There's plenty of evidence, yes.
Q. Based on that, would you agree that hypertension can and does lead to cancer?
MR. SLATER: Objection.
You can answer.
A. So you can construct a connection, I suppose, because, you know, good health, exercise will be good in preventing hypertension and also preventing cancer, so ...
In that respect, there could be a connection, sure.
Q. Is it fair to say that every plaintiff in this litigation was at an increased risk of developing cancer before they ever took a single valsartan pill?
MR. SLATER: Objection.
A. I have no idea.
Q. Are you aware of any peer-reviewed research published in the medical journals finding

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a statistically significant increased risk of kidney, colorectal, breast and other cancers in patients with hypertension?
MR. SLATER: Objection.
There's a massive lack of foundation and relevance, but you can answer the question. Plus -- I said foundation.
You can answer.
A. Not offhand.
Are you still there?
Q. Yes, I'm just thinking what I want to ask you next.
You told me that research and work that's been done over the years will tell us that cancer can be caused by many different things, one of them being smoking and tobacco use, right?
A. Yes.
Q. You identified obesity as a risk factor that can lead to cancer, right?
A. Yes.
Q. Alcohol use can lead to cancer, correct?
A. Yes.
Q. Radiation can lead to cancer?
A. Yes.

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Q. Genetics can play a role?
A. Yes.
Q. Viruses in some circumstances can cause cancer?
A. Yes.
Q. Environmental -- we believe that some environmental exposures can cause cancer, correct?
A. Yes. Yes.
Q. Are there other groups of causes that are risk factors that we haven't talked about?
A. I don't know. I think you covered the main ones. Sunlight, UV exposure I don't think you mentioned.
Q. Okay.
Given all these potential causes of cancer, are you able to look at a mutation at a cellular level and say that that mutation was caused by a specific exposure or condition?
A. That would be very difficult.
Q. So I'm only asking about you, whether you had that ability or capability.
Do you have the expertise to look at a given mutation and say this was caused by increased nitrosamine intake as opposed to genetics, as opposed to alcohol use, as opposed to

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any other factor known to cause cancer?
MR. SLATER: Objection.
You can answer.
A. I didn't quite hear your question.
Did you say patient or mutation?
Q. Mutation I said.
A. Well, some mutations are quite specific. For example, those caused by UV light, you get thymidine cross links in DNA. I'm not aware if those are caused by any other agent, so there are cases of certain mutations that are quite specific.
Q. Are you aware of any unique biomarkers caused by NDMA?
A. No.
Q. Are you aware --
A. Wait. That depends what you mean by biomarkers.
Q. Are you able to look at a mutation and say this mutation was caused by NDMA exposure?
A. No, not a mutation.
Q. Are you able to look at a mutation and say this mutation was caused by NDEA exposure?
A. No.
Q. So if there are no unique biomarkers

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for NDMA or NDEA in human tissue and given that there are multiple risk factors for cancer, are you able to state to a reasonable degree of scientific certainty that cancer causation in any of these plaintiffs in this litigation was caused by nitrosamines?
MR. SLATER: Objection.
You can answer.
A. I wouldn't say there's no biomarker. You mentioned certain mutations. But if I find -- if I'm able to obtain a DNA sample from one of the patients, for example, from their oral cells after they took a contaminated pill and analyzed the DNA in that sample and I find O6-methylguanine in that DNA, I can be reasonably sure that came from dimethylnitrosamine. So that's a biomarker.
Q. Have you obtained DNA samples from any of the plaintiffs in this case?
A. No.
Q. Have you looked for signs of O6-methylformane in any of the DNA samples or tissue samples from any of the plaintiffs in this case?
A. O6-methylguanine.
Q. Guanine.

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A. Guanine. G-U-A-N-I-N-E.
No, I haven't. But that would be a possible approach, a research approach.
Q. The presence of O6-methylguanine in a DNA sample is not the equivalent of a -- does not mean there's a carcinogenic tumor, correct?
A. Correct. But it's one step in a well-established pathway.
Q. Is the presence of O6-methylguanine specific and limited to NDMA and NDEA exposure?
A. No.
Q. Going back to my question, you told me that you cannot look at a biopsied tissue and make the determination that that mutation was caused by NDMA, correct?
MR. SLATER: Objection.
You can answer.
A. In the absence of other data, but if I had DNA from that tissue and I analyzed it for O6-methylguanine and I find O6-methylguanine and the mutation is a mutation in a raised gene and I have tissue from subjects who did not use valsartan and I don't find the mutation, that would be pretty good evidence.
Q. None of that work has been done in

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this case; is that right?
A. As far as I know.
Q. You've not done it?
A. No.
Q. What causes the presence of O6-methylguanine in a DNA sample?
A. From the metabolism of a substance such as NDMA that leads to the formation of methyl diazohydroxide, which reacts with guanine in DNA to form O6-methylguanine.
Q. My question was other than NDMA what other substances are you aware of that lead to the formation of O6-methylguanine?
A. Other methylating carcinogens, NNK, methyl methane sulfonate. I don't think there's much human exposure to that. So, you know, any methyl nitroso compound.
Q. I'm sorry. I didn't mean to interrupt you. Go ahead.
A. I'm done.
Q. Can the presence of O6-methylguanine be attributed in a DNA sample be attributed to anything other than exposure to nitrosamines?
MR. SLATER: Objection.
You can answer.

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A. Yes, it could be another methylating agent. Wouldn't necessarily have to be nitrosamine. Methyl methane sulfonate is one of the more common ones, but it's not really found in the environment.
Q. I'm going to go into this more a little later, but all of us are exposed to nitrosamines every single day, correct?
MR. SLATER: Objection.
You can answer.
A. Many people are, yes.
Q. And all of us process and develop nitrosamines endogenously.
Our body creates them, right?
A. Yes, to a certain extent.
Q. Every single day?
MR. SLATER: Objection.
A. I don't know about every single day. The measurement of endogenous formation is fraught with difficulties, but there is certainly the evidence for endogenous formation of nitrosamines.
Q. By all of us?
A. I don't know about all of us.
Q. Are you aware of any research that suggests there are some individuals that have the

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unique ability not to endogenously create nitrosamines?
MR. SLATER: Objection.
You can answer.
A. Not offhand.
Q. Right. So here's what I don't understand: If all of us or virtually all of us endogenously create nitrosamines, then every DNA sample that you are look at is going to have O6-methylguanine.
A. No, that's not true.
Q. You just said that nitrosamine exposure -- strike that.
A. Just because you're exposed to a nitrosamine doesn't mean that you'll be able to necessarily metabolize it efficiently enough to alkylate DNA. So you might have cases where the exposure is too low or the metabolism is not that efficient. It doesn't -- you can't say all.
Q. O6-methylguanine observed in a DNA sample is caused by the metabolism of nitrosamines among other things.
That's what you've told me, right?
A. Yes.
Q. When you find O6-methylguanine in a

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DNA sample, if you were to ever do this work, you would not be able to tell us whether that O6-methylguanine was from nitrosamines ingested exogenously or developed endogenously, would you?
MR. SLATER: Objection.
You can answer.
A. I could do a study that could indicate that.
Q. You've not done such a study?
A. No.
Q. No one in the world has done such a study at this point?
A. I don't know.
Q. Are you aware of any?
A. No. I could compare subjects who took contaminated valsartan and who did not and get DNA samples from those individuals and analyze them for O6-methylguanine and see if there's a difference.
Q. Okay. You could do that --
A. That would be a good start.
Q. Great.
But my question was you haven't done that scientific investigation, correct?
A. No, but I think it would be a good

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project. You gave me an idea.
Q. At least I served some purpose here today then.
I want to go back and sort of touch on one of the things that I asked you at the outset and that relates to the work that you have done in this case.
I think you told me that when you wrote your report that you acknowledged that valsartan -- whether or not nitrosamines in valsartan-containing medications were capable of causing cancer is dependent on the exposure, the dose and the duration.
Do you remember telling me that?
A. Mm-hmm.
MR. SLATER: Objection.
You can answer.
Q. You have to say "yes" or "no" for the record.
A. Yes.
Q. You gave me a general overview of some of the things that you did to try and answer the question of whether or not the exposure to nitrosamines in valsartan-containing medications was capable of increasing the risk of cancer and

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you said that one of the things you did was consult literature.
Correct?
A. Yes.
Q. How did you go about deciding upon the literature that you were going to review and cite and rely upon in your report?
A. From my experience and from staying up to date on the literature. It's one of the things that we do in research, follow the literature and attempt to read it all and use it our research and let it inform us as to our projects and conclusions. So, you know, it's important to follow the literature. It's something that all researchers do.
Q. Understood.
When you were retained by Mr. Slater back in September of 2019, did you do any or attempt to any sort of comprehensive search of the literature or did you just rely on your knowledge and efforts to stay abreast of the literature as you described it?
A. Well, I looked into the valsartan literature, but mainly I relied on my knowledge of the literature.

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Q. So if I were to --
A. But I'm not an encyclopedia, you know. I could have forgotten things here and there.
Q. Well, that's what -- I'm not suggesting you should be an encyclopedia.
Would you agree with me that formulating a meaningful and reliable opinion on a causality of exposure to a disease requires an evaluation of the totality of the evidence?
MR. SLATER: Objection.
A. Yes.
Q. So what I'm trying to get a feel for and what I'd like you to explain for me is how did you set out to make sure that your encyclopedic knowledge of the literature was adequate --
MR. SLATER: Objection.
You can answer.
Q. -- before whether it needed to be supplemented by a literature review?
MR. SLATER: Objection.
You can answer again.
A. Sure. I needed to review the available literature on valsartan, you know, the contamination with nitrosamines. I also needed to

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refresh my memory regarding dimethylnitrosamine exposures and cancer in the literature.
Q. So how do you go about refreshing your memory in that matter?
A. I go to PubMed and put in the right terms.
Q. What search terms did you use to run that query?
A. Oh, I don't remember.
Q. Do you have a list you created?
A. No, I don't have a list. I know dimethylnitrosamine and cancer. You know, it would come up with probably a thousand references and then you go from there.
Q. Were those the search terms you actually used or --
A. No. No. I mean, it's a mix. So I relied on my knowledge that's been gained over 45 years of work in this area. I've looked into the literature specifically regarding valsartan and I updated my -- refreshed my memory regarding papers looking at dimethylnitrosamine occurrence in the environment, in food, in water, etc. So I tried, you know, to cover as much as I could.
Q. I'll be honest with you, Dr. Hecht.

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I'm trying to fact check how you did your work. You said -- you told me that you would have updated your knowledge by a literature search.
Are you able to show me the actual search terms you would have used?
A. No.
Q. Are you able to show me the -- have you retained the print out of the results from your initial PubMed searches as far as what hits you received and so forth?
A. No.
MR. SLATER: Objection.
You can answer.
Q. Do you know how many publications you pulled in on your initial search?
A. No.
Q. One of the things that I asked you to bring with you or to the deposition with a notice and one of the things that your counsel was kind enough to provide to me before we began were your invoices that you've generated in connection with your work in this project.
Are you aware of that?
A. Yes.
Q. Did you provide those invoice

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documents to counsel so that he could provide them to me?
A. Yes. Yes.
MR. TRISCHLER: Can we mark those as Exhibit 4?
THE VIDEOGRAPHER: Exhibit 4 was the comparative --
MR. TRISCHLER: Exhibit 5. Exhibit 5.
THE VIDEOGRAPHER: What was the name of the document again that you wanted --
MR. TRISCHLER: Invoices.
THE VIDEOGRAPHER: Okay. Great. Would you like that up on the screen?
MR. TRISCHLER: Yes.
(Whereupon, Exhibit 5 was marked for identification.)
Q. The documents related to your invoices that we marked as Exhibit 5 consist of four pages. What we're looking at here is the first of those four pages that I have.
A. Yes.
Q. This appears to me, Dr. Hecht, to be a summary of the work that you did from at least September of 2019 through June of 2020, right?

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A. Yes.
Q. You would have billed for your work in connection with this case based on this summary, right?
A. Yes.
Q. What I'm curious about is when I read this document and look at this document marked as Exhibit 5, I don't see any reference to a literature search being done until -- well, actually in -- I stand corrected -- 12/9/19. It says "Further review and literature search on NDMA, one hour."
A. Yes.
Q. Is that when you would have done your literature search then?
A. That's what it says.
MR. SLATER: Objection.
You can answer.
Q. And your search of the literature would have taken you an hour to do?
A. On that particular day, yes.
Q. Is there any reference to any literature search on any other day in your records?
A. I don't know.

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MR. SLATER: You can go to the next page, sir.
Can you highlight that for the doctor?
Q. Is there any reference to your literature search on this page of the billing records?
A. Well, the updated report adding new text and references, so, you know, that could have involved some literature. I really don't remember.
Q. How about the next page?
A. Right. There's no reference to literature search there.
Q. How about the last page?
A. That's it.
Q. So if we look at all the invoice documents that I've been provided with, what it suggests is that there's only one reference to a literature search and that was for an hour on December of 2019.
Is that the extent of the literature search that you --
MR. SLATER: Objection.
Lack of foundation.

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You can answer, Doctor.
A. I do literature work all the time on nitrosamine. It's my part of my work.
Q. All right.
I'm talking about -- you said you keep abreast of the literature. You're looking at it all the time.
A. Yes.
Q. You're not an encyclopedia and so you did a literature search to supplement your knowledge.
Is that supplement the one hour we see in December of 2019?
MR. SLATER: Objection.
Foundation.
Argumentative.
You can answer.
A. That's what it says.
Q. You didn't -- according to your billing records, you didn't spend any other time on the literature search, right?
MR. SLATER: Objection.
You can answer.
A. I didn't bill for it.
Q. Do you remember doing it?

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A. As I said, I look at the literature almost every day in one form or another, so I don't necessarily bill for it. It's part of my work. It's part of what I do.
Q. In your report that you provided to us, you have footnotes, footnote references at the conclusion of the report, a grand total of about 146, correct?
A. Yes.
Q. It looked to me like the last -- you have that report in front of you, sir.
The last footnote, 146, is a true footnote, whereas the other 145 are citations to literature, company documents or depositions, right?
A. Yes. Right.
Q. As it relates to the -- I'm trying to distinguish for my question the scientific literature from the company documents and depositions.
Okay?
With respect to scientific literature, what was your criteria for inclusion or exclusion of literature in your report?
A. Well, the report starts with a

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general consideration of nitrosamine carcinogenesis. For that, I used literature that I refer to frequently, certain reviews and certain specific publications.
For the literature that refers more specifically to valsartan, I referred to the -- a couple of publications on valsartan as well as the EMA report and maybe a couple of others. I don't really remember.
Q. I think it's probably fair to say that your report and the references that you cite at the conclusion of the report was not intended to include citation to every publication on the subject of NDMA and NDEA ever written.
Fair to say?
A. Yes.
Q. So what I'm just wondering is was there some method in your mind that you started with as to what references you were going to rely upon and cite and which ones you were going to exclude? Did you have any methodology in that regard?
A. Yes. I focused on the studies that are relevant to cancer induction by dimethylnitrosamine in humans. Basically, I'm

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looking at the known, very well established pathways by which the dimethylnitrosamines metabolized can damage DNA, showing that that also occurs in humans, that human metabolism with dimethylnitrosamines are very well characterized.
Then looking at aspects of the exposure, putting the dose response studies that were carried out in rats, then looking at the more specific aspects of the valsartan contamination and the resulting exposure to dimethylnitrosamine and blending these together to make a logic and readable product.
Q. Were there things that you came across --
A. In order to do that, I don't need to review every publication that's ever been written on nitrosamines.
Q. Were there studies that you came across in your research and work that found the carcinogenicity of NDMA or NDEA in humans to be inconclusive or unknown that you omitted from your report?
MR. SLATER: Objection.
You can answer.
A. There are many studies that conclude

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with, you know, statements like, you know, we don't necessarily know whether this particular exposure to products or environments containing NDMA or other carcinogens for that matter actually cause cancer. So I mean, they're all -- you know, all studies have limitations and those limitations are usually described. So I mean, I would say that, you know, virtually every study that I quoted would have some kind of limitation. That's part of science.
Q. Right. It sounds like you would agree with me then that there are studies that are not included in your report that found NDMA or NDEA carcinogenicity in humans to be unknown or inconclusive that you didn't discuss or didn't cite.
A. Sure, that's possible.
Q. The studies -- many of the studies that you ultimately cite are animal studies, correct?
MR. SLATER: Objection.
You can answer.
A. Yes.
Q. I think beginning on page seven of your report you have a section titled

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"Carcinogenicity of Nitrosamines and NDMA and Cancer."
Is that right?
A. Yes.
Q. In this section of the report, you seem to cite and rely upon a series of animal studies to demonstrate the carcinogenicity of NDMA?
A. Yes.
Q. Is it true that the -- I think we talked about this a little bit in connection with your comparative paper that we mentioned earlier, but is it true that toxicity tests are often performed on animals to gain an understanding of cellular and tissue response to toxins?
A. Yes.
Q. In an animal study, do you agree that there are many factors that affect the outcome of the test or create uncertainty about its extrapolation into a heterogenous human population?
MR. SLATER: Objection.
You can answer.
A. Sure, there are uncertainties. For sure.

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Q. Genomic instability differs from species to species; true?
MR. SLATER: Objection.
You can answer.
A. Yes.
Q. DNA repair capacity differs from species to species; true?
MR. SLATER: Objection.
A. It's a very general statement.
Q. Is it true?
A. I don't know. Probably.
Q. Metabolic factors differ from species to species; true?
MR. SLATER: Objection.
You can answer.
A. Sure. There can be differences.
Q. For instance, the level of metabolic enzymes are not identical from one species to another, correct?
MR. SLATER: Objection.
You can answer.
A. In general, that's probably true.
Q. In fact, the level of enzymes are not even homogeneous across the human population?
A. Yes, that's true.

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Q. Metabolic rates also differ between humans and animals, right?
A. It can.
Q. The binding efficiency of a foreign substance like NDMA to DNA can also differ across species?
MR. SLATER: Objection.
You can answer.
A. It can.
Q. For these and other reasons, most competent scientists recognize that attempts to extrapolate data from animal studies to humans is fraught with peril?
MR. SLATER: Objection.
A. Fraught with peril?
Q. Yes, sir.
MR. SLATER: Someone wrote a good question there.
A. Strong words. Strong words.
MR. SLATER: Objection to the question.
You can answer.
Q. The question is --
A. There are uncertainties. Sure, there are uncertainties. I wouldn't say it's fraught

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with peril.
Q. Would you say it's fraught with difficulty?
MR. SLATER: Objection.
You can answer.
A. No, I wouldn't say it's fraught with difficulty.
Q. Well, let me show you --
A. I would say that -- you like the word "fraught." There are uncertainties I would say.
Q. Sure.
A. Those are well recognized.
(Whereupon, Exhibit 6 was marked for identification.)
Q. Let me show you what I'll mark as -- I think we're up to Exhibit 6. It's a paper by Gombar -- G-O-M-B-A-R -- is the lead author. The paper is entitled "Pharmacokinetics of Nitrosodimethylamine in Beagles."
Are you familiar with that paper?
A. Yes.
Q. I think you cited it in your report, correct?
A. Correct.
Q. You relied upon it, correct?

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A. Relied upon it? Sure, I cited it. Yes.
MR. TRISCHLER: Can you put up the Exhibit 6 please, the first page of it?
THE VIDEOGRAPHER: Looking for it now. One moment.
You said in beagles?
MR. TRISCHLER: Yes.
THE VIDEOGRAPHER: I'm actually not seeing this in the list I was given, one related to beagles.
THE WITNESS: Go to PubMed and enter Gombar --
MR. TRISCHLER: I'll send it now.
THE VIDEOGRAPHER: Thank you.
MR. TRISCHLER: You should have it.
THE VIDEOGRAPHER: One moment while it's downloading. That was not one that was uploaded before. Maybe it failed in the upload.
MR. TRISCHLER: Must have been the one that broke the computer.
THE VIDEOGRAPHER: Maybe.
MR. TRISCHLER: Okay.
BY MR. TRISCHLER:

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Q. So now, Dr. Hecht, we're looking at the first page of Gombar's study that you cite in your report. There's a section on the left-hand side of the first page marked "Introduction," if you could highlight that section for the doctor.
Certainly, Doctor, when I show you a document like this, you're free to read as much of the study as you want, but I wanted to direct your attention to the introduction in the second paragraph where Gombar and his colleagues note that extrapolation of carcinogenicity data from animals to humans is fraught with difficulty.
Do you see that?
A. Yes, those are the words he used.
Q. Right.
Do you agree with Gombar's statements?
A. Not necessarily. I think "fraught with difficulty" is a little too strong. You know, that's his opinion, so it's okay.
Q. But you're the one that cited to this report, not me, correct?
MR. SLATER: Objection.
Argumentative.
A. I cited it, yeah, that's true. It

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deals with the topic.
Q. And you agree with me that the attempt to -- that there are problems and limitations associated with the extrapolation of carcinogenicity data from animals to humans; true?
MR. SLATER: Objection.
A. There are limitations. Sure, there are limitations.
Q. Gombar and his colleagues go on to tell us what some of those limitations are, correct?
A. Yes.
Q. Some of those limitations include the inherited susceptiblity of tissues to the carcinogenic action of NDMA, the efficiency and fidelity of repair processes, quantitative and qualitative metabolic aspects and the pharmacokinetics of the compound may be very different in humans, right?
A. Yes. It's all true. That's why we do research.
Q. Sure.
Do you consider yourself a scientist, Dr. Hecht?
A. Yes.

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Q. As a scientist, do you agree that it's improper to draw conclusions and inferences from a study that the authors themselves did not support?
MR. SLATER: Objection.
A. I'm not -- could you repeat that?
Q. Sure.
Do you agree that it would be improper to draw conclusions or inferences from a study that the authors themselves did not support?
MR. SLATER: Hold on, Dr. Hecht.
Objection and counsel might want to read Law 360 and the Eighth Circuit's decision from yesterday.
You can answer, Dr. Hecht.
A. So we draw conclusions from our data. All the data has limitations and we think about and analyze the limitations of the data and that influences our conclusions.
Q. Do you ever draw conclusions from a study that the authors of that study themselves reject?
MR. SLATER: Objection.
You can answer.
A. Not in general. Not in general, no.

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Q. In general, you'd agree that would --
A. Well, no, actually -- so, you know, that depends on the data that's being presented. I mean, I might find errors in their data and then I wouldn't come to the same conclusions.
Q. In general, would you --
A. I might find flaws in their experimental approach and then I would reject their conclusions. Just because it's published doesn't mean that it's necessarily correct.
Q. One of the papers that you also cited was a paper by Magee and Barnes entitled -- you can take that one down -- entitled "The Production of Malignant Primary Hepatic Tumors in the Rat by Feeding Dimethylnitrosamine."
Do you recall that paper?
A. Yes, very well.
MR. TRISCHLER: I'll mark that as our next numbered exhibit. I think we're up to 7.
(Whereupon, Exhibit 7 was marked for identification.)
Q. In this paper, I believe that the rats were administered NDMA on the order of 25 milligrams per kilogram of body weight.

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Is that right?
A. Yes.
Q. Do you know how many nanograms are in a milligram?
A. Sure. There's a thousand nanograms in a microgram and there's 1,000 micrograms in a milligram, so there are a million nanograms in a milligram.
Q. So the dose that was administered to the rats in the Magee and Barnes study was --
A. Yes, that's correct.
Q. Do you know the equivalent dose of 25 million nanograms per kilogram in a human being that weighs 150 pounds?
A. Not offhand, no. I would have to do the calculation. I can't do it sitting here, talking to you.
Q. Would you agree that that dose is on order of magnitude far greater than any dose that would have been given to any plaintiff who took valsartan-containing medications containing some nitrosamines?
A. Absolutely.
Q. Do you agree that there's no correlation between the dose administered in the

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Barnes study and what any plaintiff in this case may have received?
MR. SLATER: Objection.
You can answer.
A. I don't know what you mean by "no correlation." This was, as you know, as you're well aware, the first study showing that dimethylnitrosamine causes liver tumors in rats. So naturally, they started with a high dose. That's -- if you don't start with a high dose, then you get a negative result and you still haven't answered the question.
If you start with a high dose and you get a negative result, you can be pretty sure that the compound is not a strong carcinogen. Years later, as you know, after literally many, many studies have extended and confirmed this initial study showing that dimethylnitrosamine causes liver cancer in rats, there was the study -- the dose response study by Peto, Grasso and others -- showing going down to extremely low doses.
So I don't really see what you're driving at here, sir.
MR. TRISCHLER: Object and move to strike as non-responsive.

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Q. All I was asking you about was the Magee and Barnes study, Doctor.
My question was the doses that Magee and Barnes administered to the rats in this study were far and away greater than the levels of nitrosamines that were observed in any valsartan-containing medications.
Would you agree?
A. Absolutely.
Q. And in this same study that we marked as Exhibit 7, did -- I think the authors also tried to duplicate their work on other mammals, namely rabbits, right?
MR. SLATER: Objection.
You can answer.
A. Yes.
Q. And there was NDMA that was administered to rabbits in this Magee and Barnes study, correct?
A. Yes.
Q. How much NDMA was delivered to these rabbits?
A. I don't remember.
Q. Was it --
A. It was a high dose. I think they

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also had some toxicity.
Q. Was it the same 25 milligrams per kilogram of body weight dose that the --
A. I don't know. Look in the paper. I don't remember.
Q. Do you remember that in connection with the rabbits no tumors were observed in this study?
MR. SLATER: Objection.
You can answer.
A. I forgot about the rabbits.
MR. TRISCHLER: If you could highlight the second paragraph for me, please.
Q. Take a look at it, Doctor.
Were any tumors observed in the rabbits in this study?
A. No.
MR. TRISCHLER: You mentioned the Peto paper, so let me ask you about that.
There's a paper by a gentleman named Peto that you just mentioned, P-E-T-O. We can mark that as Exhibit 8.
(Whereupon, Exhibit 8 was marked for identification.)

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Q. While the gentleman is taking care of that for us, Doctor, you not only mentioned the Peto paper a little earlier, you cited to it in your report, correct?
A. Yes.
Q. In Peto, we have another animal study where NDMA and NDEA were administered to rats, correct?
A. Yes.
Q. In his work, Peto was careful to note that no extrapolation of this data to humans should be done.
Do you agree?
A. Yes.
Q. In fact, if you can go to page 6445 of that paper, the second paragraph of the chart -- there we go -- what Peto wrote is that "It would be a serious distortion of these experimental results to extrapolate this data to humans."
Correct?
A. That's what he wrote.
Q. And so what we know from the Peto study is it provided us with some valuable information on dose response relationship to NDMA

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that was administered to rats, but it did not provide any reliable information on the effects of nitrosamines on humans, correct?
MR. SLATER: Objection.
You can answer.
A. Correct.
Q. I didn't hear your answer, sir.
A. Yes, correct.
Actually, I wouldn't say any reliable information. I hate to get into a semantic argument. I wouldn't say it doesn't provide any reliable information. It does provide reliable information, well, definitely with respect to rats. You know, whether this information is directly applicable to humans, we don't know, but it does give a strong indication of the strength of the carcinogen and a widely accepted animal model.
Q. What Peto said and what he wrote in the peer-reviewed literature was that this data does not provide reliable information as to the effects of a part per billion nitrosamine concentration on humans.
Isn't that --
A. That's what he says.

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Q. And he says it would be a distortion of these experimental results to suggest something different?
A. Yes, that's what he said.
Q. My question was not asking you about whether Peto's study provides us dose effect -- provides us with relevant and reliable dose effect data on NDMA in rats.
I'm talking about humans. When we talk about humans, Peto's study does not provide us with any reliable information. He even said so, right?
MR. SLATER: Objection.
A. That's what he says. It says it right there.
MR. TRISCHLER: I'm going to ask you about another animal study that you cited in your report. I think we'll mark this one Exhibit 9 and it's another paper by Gombar, G-O-M-B-A-R, entitled "Pharmacokinetics of N-nitrosodimethylamine in Swine."
(Whereupon, Exhibit 9 was marked for identification.)
Q. Do you see that?

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A. Yes.
Q. In this paper, is it also true, if you recall, that the authors once again cautioned against extrapolating carcinogenicity data from animals to humans?
MR. SLATER: Objection.
You can answer.
A. I don't recall, but I presume that they did.
Q. If you go to page 1353, under the "Discussion" section of the paper, first paragraph there, Gombar says once again that extrapolation of carcinogenicity data from laboratory animals to humans is a difficult task because chemical carcinogenesis is a multistep process involving many factors, right?
A. True.
Q. Do you agree with all that?
A. Pardon?
Q. Do you agree with all that, sir?
A. Yes, I do.
Q. While there are many factors that make extrapolation of data from animal studies to humans difficult, one of the things that Gombar and his colleagues note here particularly is the

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differing pharmacokinetics from species to species, correct?
A. Right.
Q. Can we agree that the authors of the animal studies that you cite in your report have repeatedly and consistently cautioned against using this animal data to extrapolate to carcinogenicity in humans?
A. They do, yeah.
Q. And there's one other statement in this Exhibit 9 that I wanted to ask you about. It's -- I think it's on the first page of the paper under the introduction section if you -- and in this study that you cite in your own report, what Gombar said and what he observes is that it's not yet proven that nitrosamines cause any human cancer.
Do you see that?
A. Yes.
Q. Do you agree with that statement?
MR. SLATER: Objection.
A. Yes.
Sorry, I just had a cramp.
Q. Are you okay?
A. Yes, I'm okay.

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Yes. I mean, that was written about 20 years ago, I think.
Q. It was written in 1988, I think.
A. Okay. So, you know, 33 years ago.
Q. Was it correct when written in 1988 that --
A. Yeah.
MR. SLATER: Let him finish the question so I can place an objection.
MR. TRISCHLER: Sorry. We have to go back to pausing there, Doctor. Sometimes -- and I know it can be difficult with the, you know, trying to do this remotely, but let me finish my question.
Q. My question was was it true, was Gombar's statement when he wrote it in 1988 that it's not yet been proven that nitrosamines cause any human cancer, was that a true and correct statement when written in 1988?
MR. SLATER: Objection.
A. Yes.
Q. And in the second -- this is the second paper that we looked at from Gombar that you cited in your report and much like the first one, can we agree that the doses that were

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administered to these animals were far greater than any human equivalent dose?
A. They were greater, yes.
Q. Far greater?
A. But not as greater as the Magee and Barnes paper. The Magee and Barnes paper, they were looking at possible carcinogenicity of a compound. They didn't know whether it was carcinogenic or not, so they started with a high dose.
In these papers by Gombar, I don't really remember the dose, but I'm pretty sure it was less than what Magee and Barnes used because this was a pharmacokinetic study. They would have used multiple doses, probably ones that were less than used by Magee and Barnes.
Q. Well, if you look at the summary of the paper there in the top left-hand column, the doses are covered.
The doses were -- there were doses of NDMA administered both intravenously and orally, correct?
A. Yes.
Q. And the doses were on the magnitude intravenously that totaled 1.6 milligrams per

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kilogram, right?
A. 0.1, 0.5 and 1.0. Those were separate. I don't know why you're adding them together.
Q. I was adding them together as a total IV dose.
A. Well, that's wrong. I mean, I think they had different animals, different specific animals that were each treated with these three different doses. In other words, the lowest dose would have been 0.1 milligrams per kilogram, not 1.6.
Q. All right.
Then the oral doses were 1.0 milligram per kilogram and 5 milligrams per kilogram?
A. Yes.
Q. There are a million nanograms in a --
A. Yes, they're higher than the human dose. We don't have to go through it again.
Q. Please let me finish my question.
A. Okay.
Q. There are orders of the doses are orders of magnitude higher than what any human would see from valsartan-containing medications,

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right?
MR. SLATER: Objection.
A. Correct. Yes, that's correct.
MR. TRISCHLER: You can take that document down, I believe, sir.
Thank you.
Q. So what we just learned from the Gombar paper was that -- and what we agreed on was that in 1988 there was no evidence demonstrating that nitrosamines caused any human cancer, right?
A. I wouldn't say no evidence. I wouldn't say that.
Q. All right. Let me rephrase the question.
A. We had evidence from -- at that time, we had evidence from tobacco-specific nitrosamines of cancer in humans.
Q. Let me ask my question specific to NDMA then.
In 1988, we can agree that it had not been proven that NDMA caused any human cancer, right?
MR. SLATER: Objection.
You can answer.
A. Yes, correct.

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Q. To this day, do you agree that there's no scientific evidence conclusively establishing NDMA as a cause of human cancer?
MR. SLATER: Objection.
You can answer.
A. Well, let me answer it this way. I'll read from the IARC report in 1978.
"Although no epidemiologic data was available N-nitrosodimethylamine should be regarded for practical purposes as if it were carcinogenic to humans," IARC, 1978, World Health Organization.
Q. Do you agree that there's no scientific evidence conclusively establishing NDEA as a known cause of human cancer?
MR. SLATER: Objection.
You can answer.
A. Yes.
Q. Can you cite me to any peer-reviewed publication available in the scientific literature identifying NDMA as a known cause of human cancers?
MR. SLATER: Objection.
You can answer.
A. No.

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Q. Can you cite me to any peer-reviewed publication available in the scientific literature identifying NDEA as a known cause of human cancers?
A. No.
Q. Are you aware of any epidemiological study that's found NDMA to be a known cause of cancer in humans?
A. Not by itself, but there are a number of epidemiology studies that looked at dietary exposure to NDMA and cancer.
Q. Have those -- are you aware of any of those studies that have concluded that NDMA is a known cause of cancer in humans?
MR. SLATER: Objection.
You can answer.
A. Not specifically as you stated it, no.
Q. Right.
There are studies that suggest there might be an association between NDMA intake and some cancers.
My question was are you aware of any epidemiological study that has found NDMA to be a known cause of cancer in humans?

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MR. SLATER: Objection.
You can answer.
A. No.
Q. Are you aware of any epidemiological study that has found NDEA to be a known cause of cancer in humans?
A. No.
Q. Have you ever seen an article or a case study published anywhere in the literature that concludes that a patient's cancer was caused by NDMA?
MR. SLATER: Objection.
You can answer.
A. No.
Q. Have you seen any article or case study published anywhere in the literature that has concluded that a patient's cancer was caused by NDEA?
MR. SLATER: Objection.
You can answer.
A. No.
Q. You mentioned the IARC report a little bit earlier.
Do you remember that?
A. Yes.

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Q. IARC is the International Agency for Research on Cancer, correct?
A. Yes.
Q. You mentioned the World Health Organization. I think IARC is an arm of the World Health Organization, right?
A. Yes.
Q. IARC has working groups that review available scientific data, prepare monographs and those monographs are then used to classify compounds as carcinogenic or noncarcinogenic, correct?
A. Right.
Q. IARC has published a monograph for NDMA you pointed out for us on the video a little bit ago, right?
A. That was an early one. It also did an update some years later.
Q. Okay. Sorry. I didn't realize you were not finished.
Were you part of the working group for the NDMA monograph?
A. No.
Q. In the monograph, the IARC working group noted that there was no case reports or

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epidemiological studies to assess carcinogenicity in humans; true?
A. Yes.
Q. IARC has also published a monograph for NDEA, right?
A. Yes. Yes.
Q. Were you part of the working group for the NDEA monograph?
A. No.
Q. In the NDEA monograph, the working group of scientists who studied this agent observed that there was no case reports available to assess carcinogenicity in humans, correct?
A. Correct.
Q. The working group also went on to note there were no available epidemiological studies to assess carcinogenicity of NDEA in humans; true?
A. Yes.
Q. So based on these monographs, IARC classified both NDMA and NDEA as Class 2A probable carcinogens.
A. Probable human carcinogens. Probable human carcinogens.
Q. Class 2A?

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A. Yes. Probable human carcinogens, not probable carcinogens.
Q. But they were assigned to Class 2A --
A. Probably carcinogenic to humans. That's what they said.
Q. Did you hear my last question?
A. 2A. Yeah, 2A.
Q. When did IARC develop this classification system?
A. I believe it was around 1970.
Q. There's a big, long list of compounds that were -- that IARC has classified since 1970, correct?
A. Yes.
MR. TRISCHLER: I don't know if we have that list or not.
On the next break, I'll have that list marked as an exhibit because I don't know if I sent it to the video folks --
THE VIDEOGRAPHER: Counsel, on that note, I have about five minutes left on this media, just to let you know.
Q. In any event, when was the Class 2A designation assigned -- first assigned to NDMA?
A. That would be 1978.

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Q. You said it was updated after 1978?
A. Yes.
Q. I think that was in 1987?
A. Sounds about right.
Q. Was the classification changed in --
A. No. Still 2A.
Q. When was NDEA first classified as 2A?
A. Same.
Q. 1970?
A. 1978.
Q. Seventy-eight. Okay.
Was it updated in 1987?
A. I believe so.
Q. When it was updated in 1987 was the classification of NDEA as a 2A class carcinogen, was it changed?
A. No. They're both 2A.
Q. To this day, has the classification of NDEA or NDMA ever changed?
A. No. Both 2A.
Q. From your perspective, the Class 1 designation is reserved for known human carcinogens, correct?
A. Yes.
Q. The known carcinogens that are

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included in Class 1 include tobacco, correct?
A. Yes.
Q. Is alcohol a Class 1 carcinogen?
A. Yes.
Q. Asbestos, is that a Class 1 carcinogen?
A. Yes.
Q. Coal?
A. Coal tar.
Q. Is listed as a Class 1 carcinogen?
A. Coal tar. Not coal itself.
Q. Okay.
The fact is IARC has identified over 100 known carcinogens, right?
A. You mean Class 1?
Q. Yes, sir.
A. I believe that's right.
Q. To this day, neither NDMA nor NDEA have ever been listed by IARC as known human carcinogen, right?
A. Not Class 1, no.
MR. TRISCHLER: We need to take a break to change tapes or do whatever the video person needs to do.
Adam, what did you want to do about a

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lunch schedule?
MR. SLATER: I want to do whatever Dr. Hecht wants to do.
MR. TRISCHLER: Okay.
Do you want to -- I'm just asking did you want to --
MR. SLATER: We'll talk during the break how much longer he wants to go before we eat.
Is that all right?
MR. TRISCHLER: It's okay with me.
THE WITNESS: I'm good until about one o'clock your time.
MR. TRISCHLER: Okay.
Why don't we take a five-minute break to do whatever the technical people need to do and we can go until one o'clock my time, if that's okay with the witness and if it's okay with Adam.
MR. SLATER: It's fine.
THE WITNESS: How long are we going to break for lunch?
MR. TRISCHLER: As long as you want.
THE WITNESS: Okay.
MR. TRISCHLER: Or as short as you

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want.
THE WITNESS: Okay. I need to go out and get something.
MR. TRISCHLER: Okay. Sure, we can -- you're in charge of that aspect, so --
THE WITNESS: Okay.
THE VIDEOGRAPHER: The time is 12:17. This ends media two.
(Recess taken)
THE VIDEOGRAPHER: The time is now 12:27.
This begins media three.
You may proceed.
Q. Doctor, before our last break, we were talking a little bit about the IARC classification of agents.
Do you recall that?
A. Yes.
Q. I asked you if there was a published list where IARC identifies all of the agents that have been studied by their grouping or classification.
Do you recall that?
A. Yes.
MR. TRISCHLER: So I've gone ahead

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and sent to our technical folks that list and I'll have that marked as the next numbered exhibit. I think it might be 10.

THE VIDEOGRAPHER: Ten is correct, sir.

(Whereupon, Exhibit 10 was marked for identification.)

Q. I think what you're now looking at is the first page of that exhibit. It's 37 pages long -- and I think if you could just blow up, Bill, some part of it for the witness's benefit -- this is the list that I was showing you or mentioning before, Doctor, and it tells us that IARC has prepared monographs for each of these agents and classified them by their carcinogenic properties, correct?

A. Yes.

Q. As we mentioned, included in this 37-page compendium is NDMA and NDEA, both of which are Class 2A, right?

A. Yes.

Q. Is it true that the classification of an agent as Class 2A is a classification that's reserved for agents where there's limited evidence of carcinogenicity in humans and sufficient

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carcinogenicity in experimental animals?

A. I think that's how they describe it.

Q. Do you agree with IARC's classification of NDMA and NDEA as Class 2A?

A. Yes, I agree. But I also agree with the statement that they should be regarded for practical purposes as if it were carcinogenic in humans. That was for NDMA.

Q. Do you agree --

A. But yes, I agree that 2A is proper because 2A is probably carcinogenic to humans. Group one is carcinogenic to humans, so you would need an instance where there's been exposure to NDMA or NDEA in the absence of other possibly causes and, you know, this could be the example, valsartan.

Q. Do you agree that there is limited evidence of carcinogenicity in humans for NDMA and NDEA?

MR. SLATER: Objection.

You can answer.

A. You know, I'm not sure about limited. So, I mean, I know that they do go through each sub category in their final evaluation. I don't really think it's -- I don't think it's limited at

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all. I don't agree. No, I don't agree.

Q. What --

A. I don't agree that it's limited.

Q. Okay.

Is there a process within IARC to petition a working group to change a classification?

A. I have no idea.

Q. At any point in your career have you ever submitted any petition, evidence or writings to IARC advocating a change in a classification for an agent?

A. No.

Q. To this point in time, have you submitted any petition, evidence or writings to IARC advocating a change in the classification for NDMA or NDEA?

A. No, I haven't.

Q. Outside the context of this litigation, have you ever submitted anything to any world health authority advocating or suggesting that the scientific evidence justified reclassifying NDMA and NDEA to known human carcinogenic status?

A. No, I haven't.

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Q. When we talk about Class 1 known human carcinogens, we mention that among the 37-page compendium there are hundreds that have been named as Class 1, right?

A. How many? I don't know.

Q. Over 100, I said.

A. If that's what you say.

Q. Okay.

A. You've got the list there.

Q. Would you agree that many of the Class 1 carcinogens are things that all of us are consuming and are exposed to on a daily basis?

A. All of them or many of them? What's your question?

Q. Would you agree that many of the Class 1 carcinogens are things that all of us consume or are exposed to on a daily basis?

A. No.

Q. Is sunlight a Class 1 carcinogen?

A. Yes.

Q. Most of us are exposed to sunlight every day, right?

MR. SLATER: Objection.

A. Unless you have xeroderma pigmentosa, yes.

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Q. Most of us don't?
A. Correct.
Q. But most of us are exposed to sunlight, a known human carcinogen, on a daily basis, right?
A. Yes.
Q. Processed meat, I think, is a Class 1 known carcinogen, right?
A. I don't know whether it's 1 or 2A.
Q. You're not sure about that one?
A. No. You can look on your list.
Q. Let me take a look.
Can you go to page 30, sir? Highlight the top third of that page for the witness. I think we can --
According to Exhibit 10 from the IARC monograph, processed meat is a group one --
A. Group one.
Q. -- carcinogen, right?
A. Group one. Yes.
Q. So the bacon that I enjoy for breakfast is a known carcinogen?
A. That would be a processed meet, yes.
Q. The deli meat that I have for lunch is a known carcinogen, according to IARC?

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A. It is, but you have to think about -- you have to read the preamble and, you know, dose is part of the picture, so you have to take that into account. When they say something is group one, they're not talking -- they're not talking about dose specifically. They're not talking about other dose that you might get when you have bacon. They're saying that, you know, processed meat, consumption of processed meat can cause cancer in humans.
Q. Sure.
It's known to cause cancer in humans according to IARC?
A. Yes, but they're not talking about the amount of processed meat. They don't do that.
Q. Everything is dose dependent?
MR. SLATER: Objection.
You can answer.
A. Most are. But, you know, the way you just stated this thing, it sounded like you weren't taking dose into account. The statement that, you know, that you made a couple minutes ago when you first brought up processed meat that -- you said something like "The bacon that I enjoy for breakfast is a group one carcinogen." Yeah,

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that's true. But everything depends on dose.
Q. I couldn't agree with you more. There are a lot of other foods and beverages that we consume every day that are Class 1 and Class 2A carcinogens according to IARC, correct?
A. Yes.
Q. The hot coffee or hot tea that we enjoy in the morning is a carcinogen according to IARC, right?
MR. SLATER: Objection.
You can answer.
A. I don't think so.
Q. Well, if we go to --
A. Coffee? Coffee?
Q. Yes, that's what I said. Hot tea or hot coffee.
A. They're talking about super heated. There are certain areas in the world where very hot beverages are consumed. It has nothing to do with what you do. Those very hot beverages can lead to cancer.
Q. Sure. Very hot --
A. Has nothing to do with your cup of coffee.
Q. Very hot beverages --

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A. Not at all.
Q. Very hot beverages above 65 degrees Celsius?
A. I don't remember the temperature involved.
Q. How does 65 --
A. I think it's higher than that.
Q. How does 65 degrees Celsius convert to Fahrenheit?
A. Nine fifth C plus 32. You do the math.
Q. I will.
Are fried foods a known carcinogen according to IARC?
A. Look on the list.
Q. I'm asking you if you know. I will.
But do you know?
A. I haven't memorized the list. I told you that.
MR. TRISCHLER: Go to page -- I'll come back to it because I can't find it right now.
Q. Is it fair to say that according to IARC most of us are exposed to known and probably carcinogens on a daily basis?

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A. I don't think IARC ever said that. I'm not aware that IARC ever made a statement like that.
Q. Let me rephrase the question. Based on the IARC classifications of agents, would you agree that most of us are exposed to known and probable carcinogens on a daily basis?
A. Well, we don't need IARC for that. I mean, you know, sunlight -- again, it's all in the dose. Everything is dependent on dose.
Q. In our lifetime, all of us are going to be exposed to dozens of carcinogens; true?
A. I wouldn't say necessarily dozens, but yes, we're all exposed to carcinogens, yes. I don't know about dozens. I don't know. I'm not sure what that means.
Q. How about multiple? Would you agree that all of us during our lifetime are exposed to multiple carcinogens?
A. Yes, multiple means more than one.
Q. So when an individual has a lifetime exposure to multiple carcinogens, do you have the basis or ability to determine the cause of cancer in any individual case?

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MR. SLATER: Objection.
A. It's challenging. Definitely challenging, but there are examples. I think I mentioned one earlier where sunlight can cause a cross linking of thymidines in DNA in individuals who cannot repair that damage. It's a specific disease called xeroderma pigmentosa. Those individuals are exposed at all to sunlight, they get skin tumors. So yes.
Q. Are you suggesting that -- it sounds like what you're suggesting is that sunlight can cause unique mutations?
A. Yes.
Q. Absent that example, when we talk about environmental exposures, do you have the ability to look at a given case and sort out multiple carcinogenic exposures and identify one as the cause of cancer in any given case?
MR. SLATER: Objection.
You can answer.
A. Sure. An example would be smokeless tobacco. I can identify exposure to an oral cavity, oral mucosa carcinogen in smokeless tobacco.
Q. Is there any such thing as a

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signature genetic lesion associated with NDMA?
A. There is a signature genetic lesion, whether that would be associated with NDMA, but there might also be other causes. So O6-methylguanine is a signature genetic lesion, a mutation in the KRAS gene, G28 transition in the second base of codon 12. That's a signature that comes from O6-methylguanine. So yes, that's a signature mutation. Doesn't necessarily come from dimethylnitrosamine as opposed to perhaps another DNA methylating agent. We don't know. But that would be a signature mutation.
Another example is in the P53 tumor suppressor gene where it's been shown that benzoapyrene and some other polycyclic aromatic hydrocarbons as well as acrolein can cause mutations at certain specific codons of the P53 tumor suppressor gene.
Those would qualify as signature mutations. So yes, there are other examples other than the thymidine cross links that I mentioned earlier. So there are examples.
Q. Maybe my question wasn't 100% clear. When I was using the term "signature genetic lesions," what I was referring to were

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lesions that would be unique to NDMA as opposed to other potential sources and it sounds like when you mentioned the P53 tumor, the O6-methylguanine and the KRAS gene, those lesions may be the result -- may be consistent with NDMA, but they might also be consistent with other causes?
A. That's possible.
Q. Right. So my question --
A. But you know, everything has to be taken in context. So, you know, I think valsartan would be a good example of a study that could be done to identify such a genetic mutation that was caused by an NDMA.
Q. But until that study is done, we can't say that the lesion is specifically caused by or related to DNA absent that scientific study?
MR. SLATER: Objection.
A. Related to what?
Q. I misspoke. I'm sorry. Absent that study and until such a study is done, we don't have the scientific ability to look at a particular lesion and say it was definitively caused by NDMA exposure?
MR. SLATER: Objection.
You can answer.

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A. No, not right now. We don't have the data. The study should be done.
Q. I asked before about NDMA.
Are you aware of whether there's any such thing as a signature genetic lesion associated with NDEA?
A. NDEA would produce the same kind of lesion in DNA O6-methylguanine, which could lead to G2A transitions in codon 12.
Q. What is that --
A. But I think there's less data for an ethylating agent, but you would certainly expect the same, the same thing.
Q. What is that opinion based on?
A. My knowledge of the scientific literature.
Q. Is there scientific literature that specifically describes the type of DNA changes that one sees in humans from NDEA?
A. Not in humans.
Q. Following the discovery of nitrosamines in some medications, you've been involved in working with the FDA, correct?
A. Yes.
Q. One of the things you mentioned in

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your report, and I think you alluded to it a little bit earlier, is that you served as a panelist in an FDA workshop in 2021, right?
A. Correct.
Q. I think that workshop was in March of this year; true?
A. Yes.
Q. And at the time you attended that and participated in that FDA workshop, you were an active consultant for the plaintiffs in this litigation; true?
A. Yes.
Q. You'd already been hired by Mr. Slater over a year and a half ago?
A. Right.
Q. How did your involvement in this FDA workshop come to be?
A. They contacted me and asked me whether because of my extensive experience and knowledge of nitrosamine carcinogenicity whether I would like to participate.
Q. When you say they contacted you, are you referring to someone at the FDA?
A. Yes.
Q. Who might that have been?

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A. I really don't remember. I could dig out the email if you really want to find out, if you want me to. I don't remember the person's name, but definitely they had contacted me.
They said there's going to be a workshop on whatever the dates were and we're planning the workshop and we'd like you to participate as a panelist or discussant. I can provide the email if you want.
Q. When you were approached by the FDA to serve on this panel, did you disclose to them your potential bias given your involvement in this litigation?
MR. SLATER: Objection.
You can answer.
A. No, I don't believe I have a bias. I don't have a bias. Definitely not. There's no bias here. It's all based on science.
Q. All right.
A. I don't know why you bring up bias.
Q. Because I'm asking --
A. Why would you do that?
Q. Because I'm asking questions, sir.
A. Okay.
Q. Did you disclose --

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A. Okay. I'm saying I don't have any bias.
Q. You said that six times, so let me ask my next question.
A. So I want to make sure you understand it.
Q. Did you disclose to the FDA that you were working on behalf of the plaintiffs pursuing claims against drug companies?
MR. SLATER: Objection.
You can answer.
A. I honestly don't remember. I may have. I really don't remember.
Q. Do you have email correspondence where you told them that?
A. I have email correspondence. Whether I told them that or not, I really don't know.
Q. I think you were one of, like, 16 --
A. I wouldn't consider it a conflict of interest at all.
Q. I think you were one of, like, 16 members of this panel, right?
A. Yeah, that's right.
Q. Was it a group of esteemed experts in their field?

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A. Yes.
Q. A group of well-respected scientists whose opinions you value and trust?
A. Yes.
Q. In addition to this workshop that you participated in with the FDA, were you also aware that the FDA has issued a number of public statements concerning the nitrosamine impurities found in drug products?
A. Yes.
Q. You've mentioned one of the things you did in your work in this case was to look into the public data and public information that was available on that, right?
A. Yes.
Q. So you were certainly aware that the FDA has made lots of public statements about the nitrosamine impurities and the significance of those impurities, correct?
A. As well they should.
Q. In those public statements, is it true that FDA has consistently observed and reported to the public that the theoretical risk of harm from nitrosamines in medications is extremely low?

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A. Yes.
MR. TRISCHLER: For instance -- why don't we mark as Exhibit 11 this document entitled "Information about Nitrosamine Impurities in Medications" that comes from the FDA website?
Can you mark that, Bill?
THE VIDEOGRAPHER: Sure thing. Just looking for it now.
(Whereupon, Exhibit 11 was marked for identification.)
Q. What you're looking at now is an eight-page document from the FDA website.
Is this one of the things you read -- do you know if this was one of the things you read in connection with your work in this case?
A. I don't recall this.
Q. Can you go to page four of the exhibit, sir? The last section has a number of bullet points. Thank you.
I don't know that this is page four that you have. At least it's not page four of mine.
THE VIDEOGRAPHER: What are you looking for on the page? This is page four

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for me?
MR. TRISCHLER: Top of the page says "What you should know about nitrosamine impurities." It's the middle box. I'm sorry. There we go. Yes. Okay. Sorry. Different printing.
Q. You can see in the middle of the page -- I think it's the fourth bullet point that we've expanded -- that reads "Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a dose that contains nitrosamines at or below acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer."
Do you see that statement?
A. Yes.
Q. Do you agree with it, sir?
A. Well, I thought that they had come out with a risk estimate. I've forgotten the exact number. So I'm a little confused by this particular statement. I'm not quite sure what they mean, "not expected to have an increased risk of cancer." It's a little confusing.

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Q. It seems to me what they're saying is at low levels, they would not expect nitrosamines in valsartan medications to cause an increased risk of cancer.
Do you agree or disagree?
MR. SLATER: Objection.
You can answer.
A. Well, I'm pretty sure they -- I don't know whether it was after this or -- I'm pretty sure they came out actually with a risk estimate of something like a one in 7,000 or something like that. So I don't know how that relates to this exactly, but I know that they -- their position was that the risk was low. So I'm aware of that.
Q. Let's start with that.
You said you're aware that the FDA's position that the risk of nitrosamines in valsartan-containing medications containing was low.
Do you agree with that statement?
MR. SLATER: Objection.
You can answer.
A. It was low compared to the benefit of the medication. So they recognize the fact that the medications are effective and that they are

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useful drugs and as I understand it, their position was that, you know, even though this horrible contamination has happened and, you know, it never should have happened, never would have been approved in any way whatsoever, but these drugs have been approved by FDA, if they had been known to contain dimethyl and dimethylnitrosamine, there's no way they would ever be approved, but the fact that it did happen and the drugs are out there now in the market, they were trying to tell people that don't stop taking your drug right now because, you know, that could have worse consequences than the nitrosamines. That's how I understand it.

MR. TRISCHLER: Object and move to strike as non-responsive.

Q. Let's look at the sentence that's up on the screen.

Do you agree with the statement that a person taking a drug that contains nitrosamines at or below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer?

A. No.

Q. Do you realize that this statement

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was prepared after the FDA had done a risk assessment on the relative risk presented by nitrosamine impurities?

A. Yeah, I'm not sure exactly about this statement -- okay? -- because I thought -- maybe I'm wrong here, but as I recall, FDA actually came out with a number based on a risk assessment exercise that was something like, you know, one in 9,000 or something like that. So I'm a little confused by this statement. I did not expect it. I'm not sure what it means, not expected to have an increased risk of cancer.

Q. Well, if the words --

A. What does that mean exactly, "not expected to"? I don't understand that.

Q. If the words "not expected" are troubling to you, I'll withdraw the question. Let me ask you something different.

Have you conducted an independent risk assessment related to nitrosamine exposure from valsartan-containing medications?

A. No, I have not.

Q. Do you understand that regulatory limits for acceptable daily intake have been established by FDA?

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A. I'm not sure how to answer that. I thought that they came up with a 96 nanograms per day. That's what they came up with, that 96 nanograms per day would be acceptable. Above that would not be.

Q. Right. That was my question.

Based on its risk assessment, the FDA established that an acceptable daily intake of NDMA was 96 nanograms per day.

You're familiar with that, right?

A. Yes, that's what I said.

Q. Based on FDA's risk assessment, it was -- they determined an acceptable daily intake of 26.5 nanograms per day was acceptable for NDEA, right?

A. Yes.

Q. You understood that those acceptable daily intake numbers were based on a lifetime exposure of 70 years, correct?

A. Yes, that's how they did the calculation.

Q. So if you do the math for NDMA, 96 times 365 times 70 leaves a lifetime acceptable exposure limit, according to FDA, of 2.5 million nanograms, right, plus change?

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A. You did it, not me.

Q. A lifetime acceptable limit of NDEA according to FDA's risk assessment would be 26.5 times 365 times 70, right?

A. Yes.

Q. And you understand, I assume, that no plaintiff in this case was taking nitrosamines containing -- nitrosamine-containing medications for 70 years or anything close to that, right?

A. Probably not.

Q. And what FDA said in its risk assessment was that exposure to roughly two and a half million nanograms of NDMA was reasonably safe for human consumption, right?

A. Yes.

Q. That's what a risk assessment is?

A. Yes.

Q. Do you agree with that risk assessment?

A. Yes, I agree with it. I mean, it's not really my area. I don't present myself as an expert in risk assessment or the calculation of risk. I don't do that. But I think it's reasonable what they did, what they came up with. It sounds reasonable to me.

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Q. But you do suggest, at least through your report, that you believe that nitrosamines in valsartan-containing medication increase the risk of causing cancer, right?
A. Yes, absolutely.
Q. And you told me that everything is dose and duration dependent, right?
A. Yes.
MR. SLATER: Objection.
Q. So you need to know if you're going to have an opinion that an exposure increased the risk of causing cancer, you need to know what a reasonably safe level for human consumption is, right?
MR. SLATER: Objection.
You can answer.
A. The safe level is zero. That's what it should be.
Q. That's not what -- not according to the FDA.
A. Well, that's okay. There's no way there should be NDMA or NDEA in these drugs. It should be zero. Absolutely.
MR. TRISCHLER: Object and move to strike because those are issues for another

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day, sir.
We're talking about causation here.
MR. SLATER: Objection.
Argumentative.
Q. Excuse me.
What the FDA said is that two and a half million nanograms of NDMA are reasonably safe for human consumption based on its risk assessment and you've not done any other assessment to say otherwise; true?
MR. SLATER: Objection.
Lack of foundation.
You can answer.
A. It's not what I do. That's true. I haven't done -- I haven't made any calculations. That's up to FDA, EMA and the risk assessors. That's not what I do.
Q. What the FDA has said is that 677,075 nanograms of NDEA is reasonably safe for human consumption and you've not done any alternative risk assessment to suggest otherwise?
A. Correct.
Q. When you sat in on the FDA nitrosamine workshop in March of this year, did you publically express any disagreement with FDA's

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risk calculation?
A. No.
MR. SLATER: Objection.
Lack of foundation.
Q. That conference was over the course of two days, correct?
A. Yes.
Q. So if you had disagreement with FDA's risk calculation, you certainly had plenty of time to offer it, right?
MR. SLATER: Objection.
A. Sure, but as I recall -- I don't really remember. I don't think the -- this particular -- I don't remember whether, you know, the risk calculation was actually discussed at the workshop. I really don't remember.
Q. Well, certainly --
A. The workshop wasn't specifically -- it was more general -- about nitrosamine exposure and carcinogenicity. Obviously, it related to drugs because that's what they do, but I don't really remember whether the risk calculation was actually discussed at that workshop. I don't think it was.
Q. Well, you've already told me that you

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are aware that the FDA, as the agency responsible for drug safety in America, has repeatedly made public statements that the health risk from nitrosamine impurities was very low.
Do you remember telling me that?
A. Yes.
Q. And the workshop that you attended in March, there was actually a transcript prepared of the whole thing.
Were you aware of that?
A. Yes, I'm aware.
Q. Do you have a copy of the transcript?
A. No. Well, it might be on my computer. I don't have a hard copy. Not here with me, no.
Q. Have you ever reviewed a transcript of the FDA workshop when you came back after it was completed in March?
A. I did review it, yes.
Q. And it was certainly discussed during the workshop, on multiple occasions, the fact that the risk from exposure to nitrosamine in valsartan-containing medications was de minimis.
That was clearly discussed, correct?
MR. SLATER: Objection.

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You can answer.
A. Yes.
Q. When you were sitting there for two days, did you ever express to anyone on that panel your disagreement with that belief?
A. No.
Q. Did you tell anyone that FDA during this two-day panel that they were wrong, that the risk of developing cancer from these small amounts of nitrosamines was actually much larger than that they believed?
MR. SLATER: Objection.
You can answer.
A. No, I told you that's not what I do. I don't do risk assessment calculations, so I would have no grounds to do that, to say that and I'm not disagreeing with the risk assessment calculations that are out there.
Q. Okay.
A. That's not what I do, so why would I say something like that?
Q. My point is that you had an opportunity in March to tell the FDA that their assessment of the risk of nitrosamine impurities in drugs being anything but de minimis was wrong

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and you did nothing about it.
Agreed?
MR. SLATER: Objection.
Lack of foundation.
Complete mischaracterization of what went on.
You can answer.
A. I think I already told you, I don't do risk assessment, so, you know, I wouldn't argue with the FDA's risk calculation. I already told you that, so why do you keep asking?
Q. I'm trying to get an answer to my question.
Did you tell anyone at FDA --
MR. SLATER: Counsel, one second.
Counsel, he's answered the question multiple times. You're beyond the point of arguing with him.
Is there some other area you want to ask him questions about --
Q. Did you tell anybody --
MR. SLATER: -- or do you want to pull the transcript out or show us the question or do you want to pull the transcript out and try to find a question

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that actually asks that question?
I'll be happy to wait for you to look for that in the transcript.
Q. Did you tell anyone at FDA their risk assessment was wrong? Yes or no?
A. No.
Q. Although you don't -- although you say risk assessments are not your business, are you aware of the fact that risk assessments, when they're performed by regulatory agencies, are intended to be extremely conservative so as to decide a patient's safety?
A. Yes.
Q. Would you agree that the establishment of a conservative, acceptable intake limit does not imply that an exposure at a higher level can cause harm?
MR. SLATER: Objection.
A. I'm not sure I understand your question.
Q. Based on what you know about risk assessments, would you agree that it is generally known and understood that those -- the establishment of those conservative estimates does not mean that an exposure at levels above what's

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determined to be an acceptable level will necessarily cause harm?
MR. SLATER: Objection.
You can answer.
A. Correct. It's based on the probability.
Q. And in fact --
A. It's all based on probability calculations.
Q. In fact, in some of the research that you cited in your report that you prepared in this case, you identified evidence and provided us with information suggesting that virtually all of us are exposed to NDMA and NDEA on a daily basis at concentrations far greater than the acceptable intakes established by FDA, right?
A. I don't know about "far greater." We are all exposed through the diet for sure.
Q. Okay.
A. I don't know about "far greater." That depends on your diet, that depends on concentrations of NDMA and NDEA and the various foods that you eat and drinking water, etc. So I don't know about "far greater."
(Whereupon, Exhibit 12 was marked for

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identification.)
Q. Let's take a look at the paper that you cited in your report from Gushgari, G-U-S-H-G-A-R-I. I think it's entitled "Critical Review of Major Sources of Human Exposure to Nitrosamines."
Do you recall this paper, Dr. Hecht?
A. Yes.
Q. Was my representation correct, that this was indeed a paper that you cited in your report that you prepared in this case?
A. It is, yes.
Q. And in Gushgari, the authors concluded that some Americans ingest as much as 25,000 to 30,000 nanograms of nitrosamines every single day, correct?
A. That's with respect to tobacco use, I believe.
Q. Right.
So smokers, according to Gushgari, consume on the order of 25,000 to 30,000 nanograms of nitrosamines every day?
A. I'm not sure whether he means smokers or smokeless tobacco users. I'd have to look at that.

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Q. Okay.
A. Then you know there's the question of whether it's nitrosamines in general or specifically tobacco specific nitrosamines or dimethylnitrosamine. I'd have to go back and look at that. So I'm not sure about that number you just gave me.
Q. Well, let's go --
A. Because the levels of dimethylnitrosamine in a cigarette are actually quite low.
Q. Well, you can certainly --
A. He was talking about nitrosamines in general, so that would include tobacco specific nitrosamines, which are present in higher concentrations. So I think that's where he got the tobacco part in his pie chart or whatever it was.
Q. Let's go to page 1130 of this Exhibit number 12, please. It's the last paragraph on the right-hand side.
One of the things Dr. Gushgari did was to estimate nitrosamine intake and nitrosamine exposure for all of us, correct?
A. Yes.

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Q. And what he said was that if you -- if tobacco use -- if you're a smoker, the rate of your nitrosamine intake is on the order of 21,800 plus or minus 4,350 nanograms per day, right?
A. I don't think it also includes smokers. I think it's smokeless tobacco users.
Q. Understood.
But what he discusses in this paper is that in addition to tobacco, our diet is also a source of nitrosamines, correct?
A. Correct.
Q. According to Gushgari, depending on what you eat, you'll consume between 1,800 to 1,900 nanograms of nitrosamine from your food, right?
A. That's what he came up with, right.
Q. Beer was another -- if you go to page 1131, I think beer was also a source of -- or potential source -- of nitrosamines according to Gushgari on the order of 1,000 nanograms per day, right?
A. Mm-hmm. Yeah.
Q. He also noted that water was a source of nitrosamines on the order of about 120 nanograms per day?

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A. Yeah, I don't know if that's -- I'm not sure about that number. Water is very low.
Q. It says -- it was highlighted.
Can you highlight it again, please?
According to the paper here, the nitrosamine exposure from water is about 120 nanograms per day, right?
A. Yeah, but I'm not sure -- there's some problems with -- there's some measurement problems with the order story having to do with artifact formation of NDMA during analysis. So I'm not sure. I don't recall whether his water calculation I think was -- may have been carried out before some of those analytical chemistry problems came to light. So I'm not sure about the water. I have to look at that more carefully.
Q. This study was done in 2018, right?
A. The review was published in 2018.
Q. Correct.
A. I don't know whether all of the water literature that he considered was before the finding that some of the water measurements were wrong. I don't know offhand.
Q. So what you're suggesting to me -- what you're suggesting to me --

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A. I'm suggesting that the water might be wrong. Everything else probably right.
Q. Might be lower than 120 nanograms?
A. Right. Yeah.
Q. I guess it would depend on the quality of the water you drink, where you get it, what the source is, right?
A. In part, but, I mean, the calculation would have to be redone based on the actual data. That's not -- that doesn't have artifacts in it.
Q. Well, so let's take water out of the equation because you said the other numbers from Gushgari are probably right.
So what his paper suggests to us is that individuals who are exposed to tobacco will consume around 25,000 nanograms of nitrosamines every single day of their life, right?
A. No, not exposed to tobacco. Use tobacco. There's a difference.
Q. Individuals who use tobacco will be exposed to 25,000 nanograms of nitrosamine every day, right?
A. That's what he came up with, yes.
Q. For those non-smokers and non-drinkers who lead a good, healthy life,

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according to Gushgari, those individuals are going to be exposed to daily levels of nitrosamines on the order of about 2,000 nanograms per day, right?
A. From food. Food and water, I guess, and beer. I don't know. The 2,000 is just from food or is it 2,000 from food plus beer plus water?
Q. Beer is separate. That's why I left it out.
A. Yeah. So what is it just from food?
Q. It says -- right in the first line that you're looking at here on the exhibit, 1,800 plus or minus 350 for a vegetarian diet, 1,900 plus or minus 380 for a Western diet.
A. Okay.
Q. So I was using 2,000 as a round number.
A. Okay.
Q. In your report, you suggest that you received information about nitrosamine levels observed in the valsartan-containing products of some of the defendants to this litigation, correct?
A. Yes.
Q. One of the defendants is Mylan, who I

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identified for you before as a company that I'm representing. You heard of that name before and you reviewed some of their data, correct?
A. Yes.
Q. If I could just direct your attention just for a second to -- I think it's page 24 and 25 of your report.
One of the things you indicate on pages 24 and 25 of your report is you had the opportunity to review information relating to nitrosamine levels that were observed in Mylan product, right?
A. Yes.
Q. On page 25, the first full paragraph, you write that Mylan's API testing confirmed NDEA levels in API batches ranging from 0.1 parts per million to 1.57 parts per million.
Did I read that accurately from your report?
A. Yes.
Q. As part of your work in this case, sir, did you take that data and attempt to calculate a mean NDEA concentration for Mylan's valsartan?
A. No, I did not.

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Q. I'll represent to you that the mean is 0.47 parts per million for all batches tested and I'll ask you to accept that number for purposes of my next question.
Okay?
A. Okay.
MR. SLATER: Objection.
You can answer.
Q. If you know the parts per million of a nitrosamine, you can convert that to nanograms by multiplying it by the dose, right?
A. Yes.
Q. In fact, you've done -- you did that calculation in various parts of your report?
A. Yes.
Q. So if we assume an NDEA concentration at the mean of 0.47 parts per million and multiply it by the highest possible dose, 300 micrograms of valsartan, we get a nanogram of about 150 nanograms per day, correct?
A. Okay.
Q. 0.47 times 320?
A. Okay.
Q. Do you agree that that math comes out to about 150?

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A. Sounds right, yeah.
Q. So taking the mean from my data of about 0.47, what it tells us is that hypothetically, a user of Mylan's valsartan may have consumed an additional 150 nanograms per day during the period he or she used the drug, right?
A. Right. Yes.
Q. So if we go back then to Gushgari's numbers, we know that tobacco users have a daily nitrosamine intake on the order of 25,000 nanograms, correct?
A. Is that his number?
Q. For tobacco users.
A. Yes.
Q. If we assume an intake now of 150 nanograms a day for Mylan's valsartan, that individual has increased their daily nitrosamine intake by a scant 0.6%, right?
A. Correct.
Q. If we take a non-smoker and a non-drinker who is living right, Gushgari tells us they will have exogenously consumed about 2,000 nanograms a day.
Do you see that highlighted?
A. Yes.

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Q. If we assume an intake of 150 nanograms per day for Mylan's valsartan, that clean-living individual has increased his or her nitrosamine intake by about 7.5%, right?
A. Correct.
Q. So what I'd like to know, Dr. Hecht, is what peer-reviewed scientific literature has ever been published to suggest that a modest one to seven percent increase in nitrosamine concentrations over a limited period of time would cause cancer in humans?
A. I'm not aware of any.
Q. In your report, you certainly don't cite any research or studies that establish a one to seven percent increase in baseline nitrosamine consumption will lead to cancer in humans.
Do you?
MR. SLATER: Objection.
A. No.
Q. And you don't cite any because no such data exists, right?
A. I didn't cite any. So if it existed, I would have cited it.
Q. Right.
And the fact is that science hasn't

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even advanced enough that the worldwide agencies classify NDEA or NDMA as known human carcinogens, right? They've never done that?
A. Well, I wouldn't say that exactly because -- go back to my book here. It says that it should be regarded for practical purposes as if it were carcinogenic to humans, 1978. 1978, but you're right.
Q. Right about what?
A. No one has said that 7.5% increase in nitrosamine exposure would lead to cancers in humans --
Q. I think it's one o'clock --
A. -- in the setting that you just described.
Q. I think it's one o'clock. I'm willing to keep going, but you had indicated you wanted to take a break at one o'clock, Doctor.
Do you want to --
A. My watch says 12:30.
Q. Okay. Let's keep going.
A. It's 12:30 here.
Q. Sorry. Let's keep going then.
So what we've been talking about so far is that exogenous nitrosamine consumption,

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correct?
A. Yes.
Q. And when we talk about exogenous consumption, we mean nitrosamines formed outside the organism, right?
A. Yes.
Q. In this case, though, with respect to nitrosamines like NDMA and NDEA, we know that they're also formed endogenously, right?
A. No, we don't really know that. We don't know that NDMA and NDEA are formed endogenously. We don't know that.
Q. Huh. Well, have you seen research suggesting that endogenous formation of NDEA and NDMA and other nitrosamines are significant?
A. Yes, I have seen such research and I believe it's wrong.
Q. Well, tell me what research you've seen to suggest that NDMA and NDEA are not formed endogenously.
A. I don't think that it's -- let's put it this way: It's hard to prove a negative. I can't cite any research that proves that they're not formed endogenously. We do know that there's very solid research that some nitroso compounds

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are formed endogenously. These are nitrosamines such as nitrosoproline that are not metabolized, so we can actually track their formation in humans by measuring them in urine because they're not metabolized.

But NDMA and NDEA present a different problem because they are metabolized, so it's very difficult to track their formation in humans.

So the endogenous formation of NDMA and NDEA is very challenging. It's very challenging to establish and I don't believe that it's been established.

Q. Well, I agree with you that it's challenging. I may agree with you that it's not been firmly established, but I think the statement you made earlier that's causing me some consternation is I believe you said that you do not believe and you are of the opinion that there is no endogenous formation of NDMA.

Is that an opinion you intend to offer in this case?

MR. SLATER: Objection.

You can answer.

A. No, I don't think I said that or if I did say that, it's wrong. What I did say is that

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in my opinion, there's no solid evidence for endogenous formation of NDMA and NDEA in humans. There are studies out there, but I believe that they're flawed.

Q. You are not aware of any study suggesting or concluding that NDMA does not form endogenously; true?

A. I'm not aware of any study that it doesn't form endogenously? Is that what you're asking? It's a double negative. Can you clarify?

Q. I'll rephrase it.

Are there any studies to your knowledge that conclude that there is no such thing has endogenous formation of NDMA?

A. No.

Q. Are you aware of any studies suggesting there's no such thing as endogenous formation of NDEA?

A. No.

Q. You're not going to offer the opinion in a courtroom in America suggesting that endogenous formation of NDMA or NDEA does not occur?

A. That's correct. I didn't say that. I never said that. In fact, what I did say was

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that there are studies out there that claim endogenous formation of NDMA and NDEA does occur. I think it's NDMA mainly. But I believe some of the methods in those studies are flawed. That's what I said.

Q. Is it true that the FDA has publically stated that the amount of endogenous formation of carcinogenic nitrosamines such as NDMA and NDEA is unknown?

A. I believe that's true. I think that was one of the conclusions of the workshop.

Q. Sure. And one of the conclusions of the workshop was that no scientist could say whether the amount of endogenous formation was equal to, less than or greater than our exogenous intake of those nitrosamines?

A. Yes, that's right. We don't know.

Q. So for all we know, if Gushgari's estimates of endogenous intake of a non --

A. Exogenous. Exogenous.

Q. Let me start over.

A. Gushgari estimated exogenous intake.

Q. Okay. I'm going to try again.

For all we know, if we use Gushgari's estimate of exogenous intake of 2,000 nanograms

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per day for a non-tobacco user, endogenous NDMA formation could be 2,000 nanograms, could be 1,000, could be 3,000 nanograms per day, right?

A. Right. We don't know.

Q. We don't know.

A. Right.

Q. Let's just assume that it's -- that endogenous formation and exogenous formation are equal to one another.

A. Why would you assume that?

Q. I'm going to ask you hypothetically to assume.

What that would suggest to us is that any nitrosamine intake for an individual who was taking valsartan-containing medications subject to a recall would be at an even lower percentage than if you had considered simply exogenous intake?

MR. SLATER: Objection.

A. Yes. Sure. If there's also endogenous formation, then the amount from the drug on a percentage basis obviously would be less.

Q. Right.

So we used Gushgari's estimates for the mean Mylan exposure and determined it to be

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0.6% to 7.5%. If we assume endogenous formation, those percentages go down.
A. Correct.
Q. How much they go down is unknown because, according to you, the scientific community doesn't know how much endogenous formation of nitrosamines takes place?
A. I don't think it's just according to me, but yes, that's true.
Q. Well, I say that because you're the only person I'm asking today.
A. Okay.
Q. You've indicated that the level of endogenous formation of nitrosamines is unknown, that there are scientists who have published peer reviewed papers suggesting that endogenous formation is quite high and far exceeds our intake exogenously?
A. Yes.
Q. One of those people was Gushgari, the guy you cited in your report, right?
A. Yes.
MR. TRISCHLER: Can you put up page 1133 of this paper? Right where you have the cursor, that paragraph right there happens to

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be the one I wanted to talk to the Doctor about.
Q. About halfway through that -- when's the last time you read this article, sir?
A. When was the last time I read it?
Q. Yes, sir.
A. Probably couple months ago.
Q. Fair to say you've read it a couple times since you wrote your report?
A. I don't really know.
Q. But you certainly would have read it before you wrote your report?
A. Yes, I did.
Q. While you cited to Gushgari in your report, you did not cite to any problems or limitations or disagreements that you had with his conclusions or analysis, right?
A. Oh, yeah. That's true.
Q. What Gushgari says here, about halfway through that paragraph that we've highlighted, he says "Recent literature suggests endogenous formation of nitrosamines governs human exposure to these compounds that may account for 97% of the total nitrosamine load."
Do you see that?

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A. Yes, I see it.
Q. So if Gushgari is right, that clean-living individual we've been talking about who takes in 2,000 nanograms per day of nitrosamines endogenously -- or exogenously is getting the other 197,000 endogenously, right?
MR. SLATER: Objection.
You can answer.
A. This is all wrong. I mean, this is crazy because he's talking nitrosamines as a class. So I mean what he's basing this on is nitrosoproline, which is a noncarcinogenic, non-metabolized nitrosamine that's been used as a monitor for endogenous formation. I'm sure that's what that calculation comes from. It had nothing to do with dimethylnitrosamine because nitrosoproline and the other nitros amino acids he's talking about are noncarcinogenic.
Q. Where does it say here that he's talking about noncarcinogenic --
A. I don't think it does. I'm sure that's what he's talking about.
Q. Did you ask him?
A. No, I didn't ask him.
Q. How are you sure that's what he's

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talking about then --
A. Because I know the literature.
Q. You have to let me finish the question, sir.
A. You asked me how I knew. I said because I know the literature.
Q. So where did Gushgari ever state that his determination that endogenous formation of nitrosamines applies only to those noncarcinogenic nitrosamines and not nitrosamines thought to be carcinogenic?
A. Thought to be carcinogenic? I don't know. I can't speak for Gushgari.
Q. We talked before about the fact that there were 300 plus nitrosamines that have been identified in the scientific community.
How many are carcinogenic?
A. Most of them. The great majority. It's not 300 nitrosamines. It's 300 nitroso compounds. Not all nitroso compounds are nitrosamines. I think the number for nitrosamines is probably closer to 150 to 200.
Anyhow, that's besides the point.
What was your question? How many are carcinogenic?

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The great majority, but not -- not the ones that we have data on for endogenous formation. Those are noncarcinogenic. Nitrosoproline and some related nitros amino acids, that's where all the reliable endogenous formation data comes from and those compounds are noncarcinogenic because they're not metabolized. They're excreted unchanged because they're polar.

Q. Did you finish your answer?

A. Yes.

Q. Endogenous formation of nitrosamines can occur with both nitrosamines that are carcinogenic and those that are thought to be noncarcinogenic, correct?

A. Yes.

Q. Have you don't any independent scientific research to quantity the levels of nitrosamines --

Strike that.

Have you done any independent scientific research to quantify the levels of NDMA that are formed endogenously?

A. No. We have not done that.

Q. Have you done any independent scientific research to quantify the levels of NDEA

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that are formed endogenously?

A. No.

Q. Would you agree that evaluating -- would you agree that in evaluating the issue of whether NDMA or NDEA actually caused cancer in humans, we need to consider that nitrosamines form both endogenously and exogenously?

A. Yes.

Q. And any intake of NDMA or NDEA from valsartan-containing medication would be just a fraction of an individual's nitrosamine load, correct?

MR. SLATER: Objection.

A. That's a very poorly phrased question, Counselor, I have to say because, again, you're mixing carcinogenic nitrosamines -- highly-carcinogenic nitrosamines, like NDMA and NDEA, with noncarcinogenic nitrosamines like nitrosoproline.

So you need to restate the question.

Q. Well, the question was any intake of NDMA or NDEA from valsartan-containing medications just a fraction of an individual's daily intake of those substances from exogenous and endogenous formation?

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MR. SLATER: Objection.

A. Of total nitrosamines, including the noncarcinogenic ones --

Q. Just those two is my question.

A. So you're saying -- you start the question or sentence -- whatever it was -- with NDMA and NDEA and you end the thought -- it's very confusing the way you said it. I mean, you have to be more specific.

Q. I was --

A. What we're talking about here is NDMA and NDEA.

Q. I agree.

In fairness, you didn't --

A. The exposure to those is only a fraction of the total nitrosamine formation, which includes the noncarcinogenic nitrosamines. We don't know whether there's NDMA and NDEA formed endogenously.

Q. Well, we do know there --

A. That's a research question.

Q. We do know there's NDMA in food?

A. Yes.

Q. We do know there's NDMA in beer?

A. Yes.

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Q. We do know there's NDMA in air?

A. I don't know about that. I don't think that that's a -- that's a blanket statement. It sounds much worse than it is. There's NDMA in food, there's NDMA in beer and there's NDMA in valsartan. We know that. There's no NDMA -- extremely small amount -- in water.

Q. Do you agree that the NDMA observed in the valsartan-containing medications is but a fraction of the NDMA to which we are exposed to exogenously and which we form endogenously?

MR. SLATER: Objection.

You can answer.

A. No, I don't. I agree about the exogenous exposure. We already went through that, the Gushgari. But I maintain that we don't know how much NDMA and NDEAs form endogenously. It could very well be zero. So we don't know. We don't know the answer to that.

Q. In the FDA workshop, was this issue of relative level of exposure from nitrosamines in valsartan-containing medications compared to our exposures exogenously and endogenously something that was discussed?

A. Yes, there was quite a bit of

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discussion about endogenous nitrosamine formation.
Q. And isn't it true in the FDA workshop the conclusion that was reached among this panel of experts was that the levels of nitrosamines as impurities in drugs are likely minuscule in comparison to exogenous exposure from foods and even more so to endogenous levels?
MR. SLATER: Objection.
A. Nitrosamines includes -- first of all, I don't think they use the word "minuscule." I'm not sure about that. I'd have to check the transcript.
Again, you're mixing apples and oranges because, as I said several times already, I think, just about everything we know about endogenous formation involves noncarcinogenic nitrosamines such as nitrosoproline. We don't have good data on the endogenous formation of the compounds found in valsartan, dimethylnitrosamine.
MR. TRISCHLER: What's your next numbered exhibit?
THE VIDEOGRAPHER: Our next exhibit number will be 13 and Counsel, just to let you know, I have about five minutes left on the media.

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MR. TRISCHLER: Please mark as Exhibit 14 --
THE VIDEOGRAPHER: Thirteen.
MR. TRISCHLER: Thirteen.
-- the document entitled "Nitrosamines as Impurities in Drugs, Health Risk Assessment and Mitigation Public Workshop," please.
THE VIDEOGRAPHER: Sure thing.
(Whereupon, Exhibit 13 was marked for identification.)
MR. SLATER: You're putting up part of the transcript here, Clem?
MR. TRISCHLER: I'm putting up a publication from the FDA titled "Nitrosamines as Impurities in Drugs, Health Risk Assessment and Mitigation Public Workshop."
Q. Do you see the first page of the Exhibit 13, sir?
A. Yes.
Q. This was a document that the FDA has published from the March 29 and March 30 public workshop that you participated in?
A. Yes.
Q. Have you read this document before?

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A. Yes.
Q. Do you agree with its content?
A. Yes.
MR. SLATER: Objection.
You can answer.
Q. Please go to page 14, last paragraph of the page.
About halfway through the page, it is written "The levels of nitrosamines as impurities in drug are likely minuscule in comparison to exogenous exposures from foods and even more so to endogenous levels."
Did I read that correctly?
A. Yes, you did. But, you know, it's a poorly written sentence, but yeah, you read it correctly. You're right, it's in the report. You're right. I read the report. I wouldn't have written it this way.
Q. It's a poorly written statement that you told me you agreed with, right?
A. Well, first of all, minuscule, I mean you said a few minutes ago, I think, from foods it was up to 7%. I think you said that. I don't know whether that's minuscule. And then even more so to endogenous levels.

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Again, this is really misleading because we don't know about the -- the nitrosamine -- the endogenous data comes almost exclusively from a noncarcinogenic nitrosoproline and related nitrosothyoproline and these compounds that's that are excreted unchanged and they're noncarcinogenic.
So, I mean, this sentence actually is a little misleading. I know it was written by the great FDA, but ...
Q. You were --
A. I was part of it. Yeah, I reviewed it. That's right. You know.
Q. You were part of the great FDA panel when this was --
A. I was, yeah. I was. Absolutely.
Q. You have to let me ask a question.
A. Okay.
Q. When this was written, did you express disagreement with it?
A. No, I did not.
Q. Did you tell anyone at FDA that this statement was incorrect?
A. No, I did not.
Q. So even if we assume for the sake of

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argument that nitrosamines like NDMA and NDEA can cause cancer in humans, what we know is that those nitrosamines can be formed both endogenously and exogenously, correct?
MR. SLATER: Objection.
You can answer.
A. I don't think there's good evidence for endogenous formation of NDMA and NDEA.
Q. I thought you told me before you were not going to express the opinion that endogenous formation does not occur.
MR. SLATER: Objection.
Argumentative.
A. Double negative.
MR. SLATER: Is there a question?
A. Double negative again. I don't know.
Can you rephrase your question?
Q. Does endogenous formation of NDEA occur?
A. I don't know.
Q. Does endogenous formation of NDMA occur?
A. I don't know.
Q. You can't rule out the possibility that endogenous formation of NDEA and NDMA occur?

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A. That is correct.
Q. In your work in this case -- strike that.
When we talk about exogenous intake of NDEA and NDMA, we know that can come from multiple sources, correct?
A. Yes.
Q. In your work in this case, have you interviewed any of the individual plaintiffs?
A. No.
Q. Have you reviewed any medical records from any of the individual plaintiffs?
A. No.
Q. Have you reviewed any questionnaires completed by any of the individual plaintiffs?
A. No.
Q. Have you prepared questionnaires to be submitted to any of the individual plaintiffs?
A. No.
Q. Have you obtained any information from any of the individual plaintiffs regarding their dietary habits, smoking history, medical history, anything like that?
A. No.
Q. Have you reviewed any of the

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depositions of any of the individual plaintiffs?
A. No.
Q. Is there any scientific means to measure the quantity of NDEA in the human body?
A. No. Not accurately.
Q. I think I asked you about NDEA. For completeness, let me ask you about NDMA.
Is there any scientific means to measure the quantity of NDMA in the human body?
A. Not in my opinion. Not right now, no.
Q. So I take it then that no such attempts have been made by you with respect to any plaintiff in this case?
A. No.
Q. So there's no way to do a blood test, a tissue sample or anything like that of an individual, look at it and say how much NDMA he or she might have in their body at any point in time?
A. I wouldn't say that. There are ways, but I haven't done it. As far as I know, it has not been done.
Q. Maybe I'm confusing myself.
I thought I had asked you if there was any scientific way to measure or quantify NDMA

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or NDEA in the body.
A. There's no established method that's accepted as far as I know, but that doesn't mean it can't be done.
Q. How would you hypothetically do it if there's no established method for doing it?
A. I would use mass spectrometry and I would use an internal standard that labeled internal standard of dimethylamine that would tell me whether any artifact formation or any other interference was occurring in the method. It can be done, but it hasn't been done as far as I know.
Q. So without some baseline, you don't have any data to establish sort of a baseline nitrosamine level for any particular plaintiff based on their exogenous and endogenous exposures to these particular nitrosamines, right?
A. No. You know, only -- well, what we already discussed, I mean, from levels in food and that kind of thing. No, not actual measurements.
Q. So without a baseline --
A. Like a before and after they took the pill or something like that, we don't have that.
Q. Right.
So without a per person, individual

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baseline, there's no -- you don't have any basis to opine whether NDMA intake or NDEA intake from valsartan-containing medications for any plaintiff in this case represented a 1%, 2%, 5% increase in their daily exposure to these nitrosamines, correct?
A. No, we don't have that data.
Q. We don't have that data for either NDMA or NDEA?
A. Correct.
Q. Are you familiar with --
A. It would be based on estimates of exposure that we know -- we know the amounts in food and beer and the things that we discuss, but actual measurements we don't have.
Q. Are you familiar with the Johnson paper on permitted daily exposure limits for nitrosamines?
A. Show me the paper.
MR. TRISCHLER: Sure. I guess it's 14 I think is what we're up to.
THE VIDEOGRAPHER: Counsel, just we're about seven minutes over.
Do you mind if we change the media?
MR. SLATER: Why don't we break for

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lunch now? We're way past --
MR. TRISCHLER: Oh, okay. Sorry about that. I lost -- for some reason, my clock on my computer is off.
THE VIDEOGRAPHER: The time is 2:04 p.m.
This ends media three.
(Recess taken)
THE VIDEOGRAPHER: The time is now 2:57.
This begins media four.
You may proceed.
(Whereupon, Exhibit 14 was marked for identification.)
Q. Dr. Hecht, are you familiar -- I'm not sure if I asked you this question before the break. I thought I was ready to introduce a paper by Mr. Johnson entitled "Permitted Daily Exposure Limits for Noteworthy Nitrosamines." I think that would be Exhibit 14.
Have you seen this paper before?
Let me know if you need it highlighted or blown up.
A. I don't recognize it.
MR. TRISCHLER: If you could, just

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highlight, Bill, the top portion.
Q. You'll note that the article was received in March of this year and accepted for publication in May.
I'm just wondering if you had a chance to review this paper or you recall reviewing this paper before you wrote your report in July of this year?
A. I haven't seen this.
Q. In this report, Johnson and his colleagues calculate a permitted daily exposure level for NDMA and NDEA.
Have you ever calculated a permitted daily exposure limit for any compound?
A. No.
Q. Are you familiar with the concept of a permitted daily exposure limit?
MR. SLATER: Objection.
You can answer.
A. Yes, in general. But I'm not sure about the language.
Q. Well, it's my understanding that in the field of toxicology, a permitted daily exposure limit generally refers to a dose that is unlikely to cause an adverse effect in an

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individual is exposed at or below this dose every day of a lifetime.
Okay?
So accepting that definition, are you -- have you ever attempted to calculate a PDE for any nitrosamine?
A. No.
Q. If you look at -- I think it's the page 302 of this paper. There's a chart or a table at the top and you'll see that in the last row or last column, Johnson and his colleagues calculated a PDE for NDMA of 6.2 micrograms and a PDE for NDEA of 2.2 micrograms.
Do you see that?
A. Mm-hmm. Yeah.
Q. We talked about the conversions before, but that equates to roughly 6,200 nanograms and 2,200 nanograms, right?
A. Right.
Q. And if you go back to the test data from Mylan that you mentioned in your report, that test data shows an NDEA range for API batches of 0.1 parts per million to 1.57 parts per million and I represented to you that the mean concentration was calculated at 0.47.

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Do you recall that?
A. What was the range again?
Q. 0.1 parts per million to 1.57 parts per million. That's what you wrote in your report.
A. Okay.
Q. And I had represented to you that that range resulted in a mean of 0.47.
MR. SLATER: Did you say NDMA or NDEA for that range you just gave?
MR. TRISCHLER: NDEA, sir.
MR. SLATER: Gotcha.
A. Okay.
Q. Converting that parts per million to a nanogram level based on the 320 milligram dose results in a nanogram concentration of about 150 nanograms.
Do you recall that math that we did before?
A. Yes.
Q. So if we use that calculation of 150 nanograms of NDEA in a tablet of Mylan's valsartan-containing medication, it's well under the PDE established by Johnson in his peer-reviewed study, correct?

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A. Yes.
Q. In fact, the mean nanogram concentration would be about 5% of that daily PDE. Correct?
A. Right. Yes.
Q. Do you have any evidence to suggest to this jury that a plaintiff in this litigation who consumed valsartan-containing medication that came from Mylan ever received a pill that contained nitrosamines above the PDE established by Johnson and his colleagues?
A. No, I don't.
Q. Earlier in the deposition --
A. No, it's still maintained that none of that should be there. It should be zero.
Q. Earlier in the deposition, I had asked you a few questions about how you went about doing your work in this case and you told me that there were, you know, three components of it: One, reviewing publically-available information about the valsartan medications; two, looking at the scientific literature; and three, reviewing documents that came to you from plaintiffs' counsel that related to documents from the manufacturer's defendants.

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Do you generally recall that discussion?
A. Mm-hmm. Yes.
Q. And you -- we talked about some of the literature that you reviewed earlier, specifically some of the animal studies, correct?
A. Yes.
Q. In addition to the animal studies, I note in your report, though, that you also discuss a number of dietary studies. I think those are primarily cited at pages 14 and 15 of your report.
Is that right?
A. Yes.
Q. Similar to what we talked about before, was there a particular method that you used to decide what dietary studies you were going to include in this report?
A. Well, I looked into literature on epidemiology studies that take into account nitrosamine exposure.
Q. Would we be able to go back at this point in time and recreate what literature you would have looked at by means of a -- the results of a literature search or notes or anything that you maintain to tell us what kind of search you

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did for the literature?
A. I didn't keep records of the -- of my literature search.
Q. I assume that you would agree with me that following a scientific approach to causation requires a review of all the relevant literature?
A. Yes.
Q. Were there any dietary intake studies that you -- addressing the potential carcinogenicity of NDMA or NDEA in foods that you reviewed beyond the ones that you listed in your report?
A. No, I don't believe so. I think they're all listed in the report. It's possible that, you know, I may have missed something, but I think they're all in the report.
Q. My apologies. I thought you had finished.
Would you agree with me that there have been many observational studies reported in the literature where scientists observe no statistically significant association between nitrosamine intake and food and the cause of various cancers?
A. No. Repeat the question.

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Q. Sure.
A. What did you say?
Q. I said have there been observational studies reported in the literature where scientists observed no statistically significant association between nitrosamine intake and food and the cause of various cancers?
A. What do you mean by observational?
Q. Well, all of these dietary intake studies are observational.
A. Well, sure, broadly speaking, but I'm not sure what you mean by observational.
Q. Let me see if I could ask another question.
A. It's a very broad term.
Q. I was trying to --
A. I'm not sure what that means.
Q. I was just trying to be sort of all encompassing with the question. Let me ask it a different way then.
There have been studies that have been reported in the literature where scientists attempted to evaluate NDMA and NDEA content in food and they reported no statistically significant association between that intake and

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cancer.
Agreed?
A. Sure. But, I mean, there are also other studies that do report an association, so I think your question should be rephrased.
Q. That was sort of my point, is that there are studies that go both ways. There are studies that have been published that report a statistically significant association between NDMA intake and some foods and the development of cancer and there are other studies that have reached a contrary result. That's the question I was asking.
A. Mm-hmm. There are both types of results -- that's true -- out there.
Q. In your report --
A. It's a very challenging study to do.
Q. Sure.
In your report, did you attempt to list or collect or identify all of those studies where no association was found between NDMA in food and the onset or development of cancer?
A. No, I did not.
Q. What it appears to me that you did -- and please correct me if I'm wrong -- again, I'm

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looking at pages 14 and 15 of your report -- what it appears to me that you did was to discuss the studies that you believe reported some association between dietary intake of nitrosamines and some cancers while ignoring any studies that reached a contrary result.
Is that accurate?
A. I focused on the ones that showed a relationship, yes.
Q. And you did not discuss the ones that don't?
MR. SLATER: Objection.
Lack of foundation.
You can answer.
A. I don't know. I mean, I may not have discussed every study in the literature.
Q. But what you did do -- and it's on page 15, if you want to take a look -- was you sort of covered the omission of non-favorable studies with one paragraph in which you said "Studies do not find a significant association or raise questions. This can be explained by smaller relatively small sample size, inadequate follow-up period to capture all cancers, bias/inadequate dose quantification, potentially mitigating

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dietary factors such as vitamin C intake and others."
Right?
A. Right.
Q. So what it sounds to me like what you're suggesting is that you're acknowledging that the dietary intake studies evaluating the role of nitrosamines in diet and the onset of cancer have gone both ways, right?
A. Yes.
Q. And what it sounds like what you did in your report is simply to say that in the studies that find no association, you discredit those by saying that they're subject to either poor study design or confounding factors?
MR. SLATER: Objection.
You can answer.
A. Well, you know, just about all of these studies can be criticized for one reason for another. I mean, these types of studies are extremely difficult to do, so they can be criticized, but yeah, I didn't cover all of the -- I didn't attempt to cover all of the studies of diet and nitrosamine content in foods and cancer. I did not attempt to do that.

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Q. And I understand --
A. But I did give examples of where nitrosamine contamination in food has been linked to cancer and there are a number of them.
Q. Right. I understand that there are difficulties in doing these studies and that they all have their limits, but when I read your report, what it suggests is that the only studies that you criticized as being limited by confounding factors are the ones that found no association between cancer and NDMA intake?
A. That's not necessarily true.
Q. Isn't that what that paragraph in page 15 means when we read it?
A. I don't know. You know, I mean, this criticism can also apply to some of the positive sides. It's a general criticism.
Q. Well, let's take a look at some of the studies that you do cite to, if we can.
Okay?
A. Okay.
MR. TRISCHLER: You cite to a study by Goodman, G-O-O-D-M-A-N, entitled "High Fat Foods and the Risk of Lung Cancer."
Can we mark that as Exhibit 15?

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(Whereupon, Exhibit 15 was marked for identification.)
Q. Are you familiar with this work, sir?
A. Yes, I am.
Q. What the authors of this study found was that there was an association between lung cancer and a diet that was rich in fats, correct?
A. Yes.
Q. They never excluded and they could not exclude was any association was due to dairy products, desserts or other fatty foods, correct?
A. I don't know about dairy products. I'd have to look at it more closely.
Q. You could look at the --
A. I'd have to read it.
Q. I can have our technician --
A. I mean do they -- I think they describe the questionnaire in there, so I have to look at that more carefully.
MR. TRISCHLER: Bill, can you highlight the top portion, please?
THE WITNESS: Yes.
Q. So what the paper says in that last sentence that was highlighted there is that what the data from the Goodman study indicates is that

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smokers with a high intake of foods rich in fat and animal protein and who have a preference for cured meats are at increased risk of lung cancer.
A. That's what they concluded.
Q. That's not really a surprising or controversial finding, is it?
A. No. A study like this would be very difficult to do in smokers. I could be critical of this study for that reason, but this is what they found and it's a good group. It's a very highly respected group.
Q. When we talk about confounding, any attempt to link these results to NDMA consumption would be limited by confounding factors relating to dietary intake of other fatty foods such as dairy products and desserts, right? That would be one confounding factor?
A. The main confounding factor would be smoking. That would blow away other confounding factors. But they found a risk in addition to smoking from cured meats and foods rich in fat and animal protein. It's a very difficult study to do. Very challenging because of the overwhelming effect of smoking.
Q. While smoking might be the primary

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confounding factor, there are others, correct?
A. Yes.
Q. By the way, the control group in this Goodman study was, I think, 326 subjects.
Was that a significant and adequate test sample size in your judgment?
A. That's relatively small by current standards. This was published in 1992, I believe. That's a relatively small sample size.
Q. Sorry.
Do you agree that a good scientist would not draw conclusions or inferences from a study that even the authors of that study would not support?
MR. SLATER: Objection.
We went through this earlier.
A. I'm not sure what that question even means. Why wouldn't the authors support their own study? I don't understand that.
Q. I said they would not support.
Can you as a scientist reach conclusions that the authors themselves do not draw?
MR. SLATER: Objection.
You went over this earlier, Counsel.

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I thought we're not going to duplicate areas of questioning in light of the time issue.
A. For this study or any study?
Q. For any study.
MR. SLATER: I object.
Counsel, you do realize you went over this entire line of questioning earlier in the deposition, right? You're just going to ignore me, I guess? Okay. Well, I don't appreciate that you're going to go through a line of questioning you already did hours ago or are you representing you didn't ask this question already and go down this line already?
MR. TRISCHLER: I've got a question pending. I'm just waiting on an answer, Adam.
MR. SLATER: You're ignoring me?
Thank you.
A. What was the question again?
Q. Is it good practice for a scientist to draw conclusions from a paper that the authors of that paper do not support?
MR. SLATER: Again, I object to this

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and I'll refer Counsel to the Eighth Circuit decision that came out yesterday that addressed this exact question and he knows it, I'm sure, and asked these questions earlier in the deposition. I don't appreciate that.
We'll take it into account if and when defense counsel asks for more than seven hours on the record with this witness.
You can answer.
A. There may be different interpretations of data. It for sure can happen.
Q. Do you agree that --
A. The authors of a paper may interpret their data in a certain way and, you know, then it's reviewed and the reviewers may agree with it, the editors of the journal may agree with it, but other scientists may not agree with the interpretation.
Q. Do you agree that a scientist should not cherrypick data from a study that might support his or her hypothesis while ignoring other parts of the study that call the conclusion into question?
A. Yes.

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Q. You also cite to a paper that was written by a gentleman named Paul Knekt, K-N-E-K-T. I'm sure I'm mispronouncing that.
But are you familiar with the paper?
A. Yes.
MR. TRISCHLER: We'll mark that as Exhibit 16, I think.
(Whereupon, Exhibit 16 was marked for identification.)
Q. You cited to the Knekt paper in your report in this case, correct?
A. Yes.
Q. Do you recall reading this study and --
A. Yes, I read it. Absolutely. I did absolutely read it.
Q. One of the first things that I note right off the bat when I read this study is in the very first sentence at the top, the authors note that the relationship of dietary nitrosamines to human cancer is uncertain.
Do you see that?
A. Yes.
Q. We talked about how some studies are difficult, some are flawed, some are well

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designed, some are not.
Was this Knekt study one that you considered to be a good, well-designed study?
A. Show me the -- show me the -- you have to show me more.
Q. Which part --
A. I want to make sure -- hold on a second.
Q. Sure.
A. Let me just look at my own notes. Yes. Okay. Yes, go ahead. What was your question.
Q. I think I asked you whether in your judgment this was a good, well-designed study.
A. Yes, it was.
Q. Can we rely on its conclusions then?
A. Yes.
MR. SLATER: Objection.
Q. In this study by Knekt, the authors observed that there was no increased risk of cancer from NDMA for any cancers of the GI tract.
Correct?
A. They found an increased risk of colorectal cancer among individuals with a high intake of NDMA. That's what it says.

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Q. Right. I didn't ask you about that, though. My question was --
A. What did you ask me then?
Q. My question was --
A. The GI tract --
Q. -- the authors observed there was no increased risk of NDMA for any cancers of the GI tract.
Is that true or not?
A. You know --
Q. I guess I should say any other cancers of the GI tract.
A. Yes, that's true. They observed for colorectal. Colorectal.
Q. They observed no increase --
A. In the first sentence of the discussion --
Q. They did --
A. -- "We found an increased risk of colorectal cancer among individuals with a high intake of NDMA and of colorectal" -- it's part of the GI tract, I think.
Q. Thank you.
They observed no increased risk of stomach cancer, correct?

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A. Correct.
Q. They observed no increased risk of esophageal cancer, correct?
A. Correct.
Q. While as you point out in this Knekt study the authors did find an association between NDMA and colorectal cancer, even those authors observed that this observation might be due to confounding, correct?
A. It's possible.
Q. It's not possible. It's what they said.
A. Yes, I'm agreeing with you. It's possible that it could be due to confounding. That's always an issue in epidemiology studies.
Q. When we talk about dietary studies like this and others that you cited and reviewed, they're all based on self-reported dietary behavior, correct?
A. No. Yes. Yes, they are. Yes and no. Okay? So I mean in some of these studies -- so they, you know, the subjects fill out questionnaires about diet. That's self-reporting. But the investigators used data -- very extensive data -- on dimethyl and dimethylnitrosamine in

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food in order to make the calculations. So it's not like somebody self-reports, you know, I don't think I was exposed to much dimethylnitrosamine yesterday or anything like that. It's the self-reporting for the kinds of foods that they -- which is pretty reliable.
So they ask the subjects -- you know, they could give them a big table of different types of food and methods of preparation, everything, and the subjects fill out these questionnaires so that the investigators know basically what the person's diet consisted of.
Then they use that information and tables which are developed by the government agencies in that country -- for example, in Europe, by the EU -- tables that give the nitrosamine content of many different types of food in great accuracy and they combine this information with the personal dietary information. It's not like they're asking people "Did you consume any nitrosamines today?" The people answering the questions have no idea. They're just -- they're just explaining what their customary diet is, which people can do with great accuracy. This is particularly true in cohort

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studies where you're interviewing healthy people and then following them for years.
Q. Have you finished your answer?
A. Yes.
Q. Have you seen any of the questionnaires that were used in the Knekt study that were talked about right now?
A. No, I didn't see the actual questionnaires.
Q. Have you seen any of the --
A. I did not.
Q. Have you seen any of the questionnaires in any of the studies that you cite in your paper?
A. No, I haven't seen the actual questionnaires, but I'm familiar with -- I'm familiar with epidemiologists, I'm familiar with the general topic of diet and cancer from my previous experience in cancer research and from having served on study sections and having been involved in evaluations of areas -- lifestyle habits and cancer, etc., etc.
So I've been in a lot of -- I've been on many different committees that have evaluated this kind of work. I've worked with

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epidemiologists, so I'm familiar with diet and cancer studies and the approaches that are used, but I didn't see the -- I didn't see the particular diet questionnaire that was used for this study or for any of the other studies for that matter.

MR. TRISCHLER: Object and move to strike as non-responsive.

Q. Did you see any of the tables that were used to estimate NDMA exposures in the Knekt study?

A. I didn't see the tables themselves, but I'm familiar with this kind of table.

Q. I didn't ask if you were familiar --

A. All right.

Q. I said did you --

A. You asked me the question. Okay?

Q. Right --

A. So I'm telling you I'm familiar with the studies that are done, the kind of tables. All right?

Q. I appreciate that, but I'm entitled to answers to the questions I ask.

Did you see the tables that were used --

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A. No.

Q. Did you see the tables used in any of the studies that you cite to calculate nitrosamine or to estimate nitrosamine exposures?

A. I did not see the actual raw data tables, no. I depended on the published studies. The published information.

Q. In all of these --

A. But I'm familiar with the kinds of tables that they're using. I am a consultant for the FSA. That's the European Food Safety Authority. I'm familiar with the kinds of data they have and that's the kind of data that was used in these studies.

Q. Are you finished?

In any of the studies that you cite, is the actual NDMA content in the foods consumed by the subjects ever measured?

A. Not in the specific foods, but in the categories of foods, yes. Definitely.

Q. Measured by whom?

A. I can't give you an answer to that question, but going back to what I said before, FSA and others have consulting laboratories that make these measurements using well-established and

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well-developed methods.

Q. You said you worked with FSA and are working with them right now, correct?

A. Yes, that's right.

Q. Have you seen FSA publications estimating NDMA content in various foods?

A. We're working on it.

Q. You're working on it? Have you seen --

A. I've seen the data. Yes, I've seen the data.

Q. Have they ever published any of it?

A. Not yet, no.

Q. Okay.

So if FSA hasn't published any of its data, none of the authors of any of these papers would have ever used it, correct?

A. No, no, no. They published data before. I'm talking about this particular report. There's plenty of published data on nitrosamine levels in food and plenty of unpublished data also by government regulatory authorities.

Q. I'm asking you about FSA because you brought them up.

A. Yeah. I'm telling you what they're

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doing now.

Q. Try to let me ask the question, please.

A. I'm not sure exactly what they were doing at the time of some of these other studies, but there's plenty of -- there's plenty of data out there, reliable data on nitrosamine content in various foods.

MR. TRISCHLER: Object and move to strike as non-responsive.

Q. Sir, has FSA ever published any data on nitrosamine -- on nitrosamine levels in foods?

A. I believe they have.

Q. Have you ever seen it?

A. Maybe.

Q. Do you have it?

A. I don't have it in my hands. I'd have to look -- FSA has the so-called FSA Journal where they publish a very detailed compendium and it's very likely that there's something in there on nitrosamines in food, but I can't cite it offhand.

Q. One of the things that --

A. You know, you can look. Look in the FSA Journal.

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Q. One of the things that you and I talked about a few minutes ago was that the dietary studies have been inconsistent in terms of knowing an association between dietary intake of nitrosamines and cancer, correct?
A. Yes.
Q. And just by way of one example, you cited to a paper that was published by an author named Loh, L-O-H.
Do you recall that paper?
A. Yes.
MR. TRISCHLER: One thing I wanted to ask you about is if you -- we'll mark that as Exhibit 16, I think, and 17 maybe.
THE VIDEOGRAPHER: We're on 17.
(Whereupon, Exhibit 17 was marked for identification.)
MR. TRISCHLER: If you go to 1057 of that document, please, the first paragraph of text below the table, can you highlight that for the benefit of the witness?
Q. Are you able to see what is on the screen, sir?
A. Yes.
Q. I see that you referred earlier to

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some notes and you pulled out, I'm guessing, some notes. It appears you're looking at something. What are you looking at now?
A. I'm looking at the Loh paper.
Q. Before you mentioned that you had some notes when I think I was asking you about the Knekt paper we had out before.
Do you have notes that you took from your review of these studies?
A. What do you mean, notes? I read the papers and, you know, I underlined and circled certain passages.
Q. Did you write any notes based on --
A. No, I didn't write any notes. No.
Q. So what you have in front of you then is just a binder of studies?
A. Yes.
Q. Are there any studies -- thank you.
Are there any studies in the binder that are not cited in your report?
A. No. All of these come from my report.
Q. And the only markings that you made in your review then are highlighting and circling or underlining those types of things?

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MR. SLATER: Objection.
That wasn't the testimony.
You can answer.
A. What's your question?
Q. I'm trying to understand when you made reference before that you wanted to "pull your notes," I'm trying to understand what you meant by notes.
A. Yes. The binder. I read the papers in the binder and as I read them, I circled or underlined certain statements that I thought might be relevant.
Q. Did you write any text --
A. No.
Q. -- in those notes?
A. No, I did not.
Q. So if we -- what we're looking at now on Exhibit 17 is a part of the Loh paper. It looks like you have the actual paper in your notebook, correct, or binder?
A. This is American Journal of Clinical Nutrition.
Is that the one you're talking about?
Q. Yes, sir.
A. 2011?

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Q. Yes.
A. Yes.
Q. What we were talking about before, again, is how the studies have been inconsistent and that's one of the things that Dr. Loh observes in this paper, correct?
A. Yes.
Q. Basically, as we look at -- as we're looking at right here, what Loh observed was that there'd been published studies with respect to gastric cancer that go both ways. Some report a positive association with gastric cancer, while others do not, right?
A. Insufficient evidence for esophageal cancer, but a positive association between nitrosamine intake and gastric cancer. So I think you said -- I don't think that's what you said.
You said a positive association between nitrite and nitrosamine intake and gastric cancer. That's what Loh is saying. Not what you said. Insufficient evidence for esophageal cancer. I think you said --
Q. I'm looking at --
A. -- both positive and negative --
Q. I'm looking at the sentence that says

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in his review -- "In this review, cohort studies reported no association for nitrite and NDMA intakes with gastric cancer risk."
Do you see that?
A. Cohort studies. Right. Cohort studies.
Q. Right. That's what I'm saying.
The studies on gastric cancer and NDMA have gone both ways. Some have said there's an association, others have found to the contrary.
A. Correct. Correct. You're right.
Q. Loh is simply reporting that, correct?
A. Yes.
Q. In Loh's own study, it goes on to note that they did not find a statistically significant association between NDMA and colon cancer, right?
A. I think they found association with rectal cancer, but not colon cancer.
Q. Correct.
They found no association with gastric cancer?
A. Correct.
MR. SLATER: Objection.

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You went a little quick again. Just give me a second to object.
I object to the foundation of that question.
Q. And Loh's work did not support and cannot be cited for support for a statistical association between NDMA and esophageal cancer, correct?
A. Correct.
Q. Not only are the dietary study results conflicting, but the authors of those studies have even acknowledged that they're not reliable in attempting to establish causation of cancer, correct?
A. Where is that?
Q. I'm asking. I'm not saying it's in this paper. I'm just asking --
A. I haven't seen that they said it's not reliable. Maybe you know where that is, but I haven't seen it. Where the authors of the study said their study was not reliable? I haven't seen that. If they didn't think it was reliable, they wouldn't try to publish it.
Q. The question that I was asking was a little bit broader than that. I was simply asking

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you if you would agree with me that given the inconsistencies that have been observed in the findings in these dietary studies that one cannot rely on those studies to suggest a causal connection between NDMA intake and cancer.
A. No, I do not agree whatsoever.
Q. Are you familiar with --
A. There's plenty of evidence from these studies. It's not totally consistent in the sense that different tissues are implicated in different studies, but there's -- overall there are a number of -- particularly, the cohort studies, particularly those that have information on exposure that do indicate a connection between dietary nitrosamines and cancer. I don't agree with you.
Q. Okay.
Here, we're looking at an analysis of cohort studies by an author of a paper that you cited that says there's no association with NDMA and gastric cancer.
A. Gastric cancer.
Q. And you agree with that?
A. What I said was that there are cohort studies that show an association between NDMA and

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cancer, GI cancer. Not necessarily gastric cancer. GI tract, colon, rectum --
Q. Are you familiar with the --
A. -- and others.
Q. -- song, S-O-N-G, paper?
A. Yes.
Q. It's entitled "Dietary Nitrates, Nitrites and Nitrosamine Intake and the Risk of Gastric Cancer, a Meta Analysis"?
A. Yes.
Q. What's a meta analysis?
A. Meta analysis, they combine data from multiple different studies and combine them into one statistical package that they use to do the analysis. So it enables you to have a much larger number of subjects than you would in a single study.
Q. So Song pulled data from a lot of different studies?
A. Yes.
Q. Isn't it true --
A. Eleven studies.
Q. Okay.
Isn't it true that they -- that the authors of the Song paper concluded that they

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could not confirm the reliability of any conclusions with respect to an association between NDMA and cancer?
A. I have to look at it. I have to look at it.
Q. It's up on the screen. We could go to page 9893, if you'd like.
MR. SLATER: Hang on, Counsel.
Of course if Dr. Hecht wants to look through the study before you continue, he's allowed to, right?
MR. TRISCHLER: Of course. I was just --
MR. SLATER: I think that's what he was doing.
MR. TRISCHLER: He could look if he wants. He could read the whole thing if he'd like.
MR. SLATER: Okay.
THE VIDEOGRAPHER: Counsel, sorry to cut in. You didn't announce you were going to mark this. Would you like this marked as the next one?
MR. TRISCHLER: Sure.
(Whereupon, Exhibit 18 was marked for

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identification.)
THE VIDEOGRAPHER: This is Exhibit 18.
Do you want me to jump to 9893?
MR. TRISCHLER: He seems to be reading it. If he wants you to, you can. We'll let him read it --
A. It's right in the abstract. The summary relative risk of stomach cancer was 1.34 for NDMA. It's in the abstract.
Q. So you read the abstract?
A. I read the whole paper.
Q. I'm sorry?
A. Huh?
Q. I said you read the abstract, correct?
A. I read the whole paper.
Q. All right.
Did you read the conclusion that appears on page 9893?
A. Dietary nitrates intake was associated with a reduced risk of gastric cancer and high consumption of nitrites and NDMA could increase the risk. They go on to say that they could not absolutely confirm the reliability of

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the findings, which of course is applicable to many epidemiologists, particularly diet and cancer.
Q. Can we agree even though those instances where a study notes or observes an association that that association does not establish causation?
MR. SLATER: Objection.
You can answer.
A. That depends on the study. I think if we look at things like smoking and cancer and UV and cancer where, you know, the relative risks are extremely high, then you say yes, causation. And, you know, you have to take into account all of the data. So if we have a situation where there's exposure to a carcinogen, which has well-known carcinogenic effects on very low doses, such as NDMA, and can be considered, it should be regarded for practical purposes as if it were a carcinogen to humans, then yes, that equals causation.
Q. Let me be more specific.
Have you seen any paper published in the literature that suggests that the -- that there's a causal connection between exogenous NDMA

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intake and the -- and the cause of cancer in humans?
A. Yes. We just discussed -- what we've been talking about the last hour.
Q. Show me where it says that these exogenous NDMA intake in diet cause cancer. Where does it say that, sir?
A. Causes cancer?
Q. Yes, that was the question.
A. No. The language is much more cautious, of course. It has to be.
Q. I'm asking you has there ever been a paper published where it's been concluded that NDMA -- exogenous NDMA intake in food caused cancer?
A. I would say collectively the papers that we reviewed indicate that NDMA in food does cause cancer. Otherwise, they wouldn't have seen these elevated relative risks in all of these different studies, some of which were very large.
Q. Show me a -- find me a statement in any of the papers in your notebook where that conclusion was made by an author of a published study?
A. There isn't. That cause cancer?

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Q. Right. It's not --
A. It did not say that.
Q. It's never been written in the scientific literature that dietary intake of NDMA has caused cancer; true?
A. In humans.
Q. In humans. Correct.
A. Caused cancer, correct.
Q. Never been --
A. You can't --
Q. Never been written --
A. There's still not enough data to say absolutely cause cancer.
Q. You've got to let me ask a question, sir.
It's never been written anywhere in the scientific literature that dietary exposure to NDEA has caused cancer in humans, has it?
A. Now you're on NDEA?
Q. Yes.
A. Okay. I thought you were talking about NDMA.
I do not believe that there is such a study, yes, where it says NDEA caused cancer in humans. I don't think there is such a study in

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the literature.
Q. Did you suggest to me and to this jury a little bit ago that the mere association between NDMA and cancer is enough to establish causation? Is that what you want us to believe?
A. I'm saying that there are a number of strong studies where we have good solid dose information and we have good solid information on cancers that occurred and the study design is strong, such that collectively they present a conclusion that NDMA can cause cancer. Whether it does cause cancer, I would say it still needs research.
Q. By the --
A. I go back to this again.
Q. By the same token --
MR. SLATER: For the record, that was referring to the 1978 IARC publication?
THE WITNESS: Yes.
Q. By the same token, those same studies in the literature include many studies where there have been no association observed between NDMA and cancer, correct?
A. I don't know about many. There are some.

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Q. We've looked at a few, right?
A. No. We looked at a number of different studies. You know, there are both positive and negative results depending on the tissue or organs being looked at and depending on the study. It's a mixed bag.
Q. So since the dietary literature is a mixed bag, as you called it, what methodology did you employ to make the leap from an association between NDMA and cancer in some studies and causation?
MR. SLATER: Objection.
Foundation.
You can answer.
A. I take into consideration the high carcinogenicity of NDMA in animal models able to induce tumors and I think something like 28 different animal species, even at very low doses as shown in rats. I combine that with the study design of the prospective studies and the very reliable dietary information on NDMA in food and I conclude that this is collectively a very strong link.
Q. Are you familiar with the Bradford Hill criteria?

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A. Yes.
Q. Do you recognize that the Bradford Hill criteria is a recognized methodology that's used to evaluate whether an observed association rises to the level of causation?
A. Yes.
Q. Are you familiar with the actual Bradford Hill criteria?
A. Yes.
Q. Can you cite any of them for me?
A. I don't have them memorized, but we could pull it up if necessary.
Q. It's not a memory test. I was just asking if you know any --
A. Thank you.
Q. -- offhand.
A. Consistency is one of them.
Q. There's nine of them total, right?
A. I thought you said it wasn't a memory test.
Q. It's not. I'm just asking if you know the number of them.
A. So why don't you just pull it up then if you want to talk about it?
Q. Did you employ the Bradford Hill

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criteria in this case or utilize the Bradford Hill criteria to determine whether the strength of association in some of these studies merited making the leap to causation?
A. No, I did not.
Q. Did you use any methodology that's described in the scientific literature to assist you in making your causation determination or was it simply your own methodology?
A. I'm familiar with the methodology for the analysis of nitrosamine in foods and I know that there are very good, very thorough databases on nitrosamines in food.
I'm familiar with the methodology used in epidemiology prospective so-called cohort studies. I'm familiar with those things and I'm also familiar with the animal data on nitrosamines and the dose response data for dimethyl and several other nitrosamines from animal studies. So I'm very familiar with all of this literature.
It doesn't -- it's not something that I just started reading about, you know, to prepare for this deposition. This is something I have been involved with for more than 45 years, so I'm quite familiar with the field. I watched the

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field evolve. I'm familiar with the evolution of all of the animal data and the evolution of all of the analytical chemistry data which in the early days was plagued by artifacts and other problems, but now is known to be extremely reliable.
So when I put all of this data together and looking at it in comparison, looking at it in context of the firm highly reliable data that we have, put that together with the use of an epidemiologic study design, with the cohort study, I'm quite confident in the results of these studies and after having reviewed them all, my conclusion is that yes, there is definitely causation. That's my conclusion.
Q. And your conclusion was based on the fact that you're familiar with the literature and you're familiar with nitrosamines, right?
A. More than familiar. I would say that I have lived nitrosamines for more than half my life.
Q. So you drew conclusions from the literature based on your -- given that you're familiar with it and experienced in the subject?
A. Yes.
Q. But you did not follow any recognized

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methodology for making the leap from association to causation?
A. It was not a formal --
MR. SLATER: Objection.
One second, Doctor. Doctor, one second.
Objection. That's a gross mischaracterization and it's argumentative at this point.
Do you want him to walk through his methodology again for you, Counsel --
MR. TRISCHLER: Sara, did you get the answer?
MR. SLATER: Let me finish, please.
-- or do you want to keep saying things regardless of what you heard?
MR. TRISCHLER: Sara, did you get the answer?
(Whereupon, the record was read back by the reporter.)
Q. Did you want to finish that answer, Doctor?
A. It was not a formal evaluation.
Q. In your view of this case and based on your knowledge of all the relevant literature

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which you've told us that you have, did you find a single epidemiological study that concluded that exogenous intake of NDMA was the cause of bladder cancer in humans?
MR. SLATER: Objection.
A. Bladder cancer? I don't think I saw bladder cancer.
Q. In your review --
A. I don't think that's been reported.
Q. In your review of all the literature, did you find a single peer review study that concluded that exogenous intake of NDMA was the cause of blood cancer in humans?
A. No.
Q. In your review of all the literature, did you find a single peer-reviewed study that concluded that exogenous intake of NDMA was the cause of breast cancer in humans?
A. No.
Q. In your review of all the literature, did you find a single peer-reviewed study that concluded that exogenous intake of NDMA was the cause of colorectal cancer in humans?
A. Yes.
Q. My question was cause, not

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association.
Did you find any papers that suggested that exogenous intake of NDMA was the cause of colorectal cancer in humans?
A. We just reviewed -- we just did this. I mean, I don't know. I don't know what you're getting at here.
Q. I'm distinguishing between --
A. We just did this and we just discussed all of this, so I don't know what you're trying to get at.
Q. Well, let me try and help you out, if I can. I'm distinguishing between a study that notes an association and a published study that makes a determination or statement regarding cause.
So my question is are you aware of any peer-reviewed study that concluded that exogenous intake of NDMA was the cause of colorectal cancer in humans?
A. No.
Q. Are you aware of any published study that concluded that exogenous intake of NDMA was the cause of esophageal cancer in humans?
A. No.

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Q. Are you aware of any peer-reviewed published study that concluded that exogenous intake of NDMA was the cause of gastric cancer in humans?
A. Cause? No.
Q. Are you aware of any peer-reviewed study that concluded that exogenous intake of NDMA was the cause of kidney cancer in humans?
A. No.
Q. Are you aware of any peer-reviewed study that concluded that exogenous intake of NDMA was the cause of liver cancer in humans?
A. No.
Q. Are you aware of any peer-reviewed studies that concluded that exogenous intake of NDMA was the cause of lung cancer in humans?
A. No. Not cause, no.
Q. Are you aware of any peer-reviewed study that concluded that exogenous intake of NDMA was the cause of pancreatic cancer in humans?
A. No.
Q. Are you aware of any peer-reviewed study that concluded that the exogenous intake of NDMA was the cause of pharyngeal cancer in humans?
A. No.

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Q. Are you aware of any peer-reviewed study that concluded that exogenous intake was the cause of -- exogenous intake of NDMA was the cause of prostate cancer in humans?
A. No.
Q. Are you aware of any peer-reviewed study that concluded that the exogenous intake of NDMA was the cause of uterine cancer in humans?
A. No.
Q. I'm going to ask you a questions now about NDEA as opposed to NDMA.
A. It's all the same answers. You don't have to go through it.
Q. If we listed all 13 of the cancers that are at issue, are you aware of any peer-reviewed study that concluded that exogenous intake of NDEA was the cause of any of those cancers?
A. No.
Q. Do you agree or disagree with this statement, Doctor: DNA adduct formation alone is inadequate to confirm mutation or cancer?
A. Agree.
MR. SLATER: Objection.
You went a little quick again.

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Are we going back over this again? I thought we --
MR. TRISCHLER: You cut out, Adam. I couldn't hear you.
MR. SLATER: Can you hear me now?
MR. TRISCHLER: Yes.
MR. SLATER: I said objection.
I thought we covered this hours ago.
Q. Are you familiar with MGMT?
A. Yes.
Q. Is MGMT a DNA repair enzyme?
A. Yes.
Q. Is it one of those things in our body that allows us to fight off mutagens?
A. No, it doesn't act on mutagens. It acts on DNA adducts, specifically O6-methylguanine. So O6-methylguanine DNA methyl transfers. Therefore the name MGMT.
Q. Do you agree or disagree with this statement: Risks from nitrosamines in drugs is likely to be very low because depletion of MGMT is not expected?
A. I don't necessarily agree with that, no.
Q. What would be your --

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A. I don't agree with that.
Q. What would be your basis for disagreeing?
A. Well, MGMT activity might be low for a number of reasons. It may have been MGMT activity may have been used up by other exposures, so, you know, if there is O6-alkylguanine form from various different exposures, some of which we may not be aware of, MGMT can be used up tending to those exposures.
Q. Do you --
A. So I don't think we know -- we don't really know, you know, how much MGMT activity a person has in reserve to address nitrosamine exposure. We don't have that information.
Q. So long as there's no MGMT depletion, one would not expect that a low-level nitrosamine exposure would lead to the development of mutagens, correct?
MR. SLATER: Objection.
You can answer.
A. No, I don't think that's correct. I mean, nitrosamines do a lot of things to DNA. It's not just O6-methylguanine. Dimethylnitrosamine forms multiple different

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adducts in DNA. O6-methylguanine has been studied most extensively because we know that it has miscoding properties. We know that it can lead to mutations. We know about MGMT, we know that it's -- well, it's not the major DNA damage caused by nitrosamines by any means. It's actually one of the minor ones. So there's a lot of other damaged DNA that can lead to mutations and cancer. It wouldn't be addressed by MGMT.
Q. Have you ever studied MGMT depletion in humans?
A. No, I honestly have not studied it. My group has not studied it. There's a fair amount of literature on it. There's a large amount of literature on it, particularly in the chemotherapy literature because MGMT can act on chemotherapeutic drugs, decreasing their efficacy, so people looked for inhibitors of MGMT to be used as co-factors in chemotherapy.
Q. I want to go back and do a little housekeeping, just to make sure that I have an understanding of everything that you reviewed and relied upon to put together your report and come to your conclusions.
Okay?

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A. Okay.
Q. You -- we talked about how you were retained by --
MR. SLATER: Counsel, excuse me, I don't mean to interrupt, but are you now going to rehash the testimony from six hours ago? I don't understand what we're doing.
MR. TRISCHLER: You probably couldn't understand what I'm doing since I haven't asked a question yet.
MR. SLATER: Well, no, but you started to ask about, you know, you're back to the beginning. I don't think it's a reasonable predicate to say "Well, I just want to make sure I understand ..." and then go over testimony you took in great detail in the questioning. I ask you not to duplicate that questioning, please.
MR. TRISCHLER: Well, since I haven't asked a question yet, I don't know how it could be duplicative, but if you think it is, I'm sure you could object to it on that basis.
MR. SLATER: Well, it's your obligation not to do so, so don't put it on

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me, please.
Q. You told us that you reviewed documents that were provided to you by counsel.
Do you recall that?
A. Yes.
MR. TRISCHLER: I'm going to mark as an exhibit the next number that we're up to, a document that I think was attached to your report. It's called "Documents Reviewed" and it's Exhibit 2 to your report. I'm going to mark it as a separate exhibit here.
Can you put that up, Bill, please?
THE VIDEOGRAPHER: Just looking for a document that matches that description.
Just give me one moment.
THE WITNESS: It's B. It's addendum B.
THE VIDEOGRAPHER: I'm seeing a document that was uploaded. The name of the document is reviewed -- got it. Sorry about that. That will be Exhibit 19.
(Whereupon, Exhibit 19 was marked for identification.)
Q. This is a document that you prepared and provided in connection with your report,

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correct, sir?
A. Yes.
Q. All I'm trying to confirm is is this a list of documents that were provided to you by counsel in connection with your review and your work in this case?
A. Yes.
Q. I think that -- and to be fair, when we get to the last -- the second-to-last page, there's a section marked "Regulatory Documents" and you had indicated before that, you know, in addition to looking at company documents and the public literature, you also looked at public materials about the valsartan medications, correct?
A. Yes.
Q. Would this be a list of those public documents that you reviewed?
A. Yes.
Q. Is there -- other than what's on this six-page list -- and please feel free to go through it if you need -- but are there any other documents that you reviewed or received in connection with your work in this case prior to the time you sat down and wrote the report that we

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marked as Exhibit 1?
A. No. The list is complete.
Q. I was told that you also -- it was delivered to me yesterday, six binders of materials that was delivered to me electronically and there was a table of contents with those binders.
Have you ever seen those tables of contents?
A. I think I know what you're referring to. I mean, in the binders, the binders have a table of contents.
MR. TRISCHLER: I don't know if we have these in the chat or available, but I was going to mark the table of contents in the binder as the next number of exhibit, just so we have a record of what his file materials consist of. Okay?
MR. SLATER: Yeah, I mean all those materials you have already and have had. Those were just provided to him for his convenience, in case he wanted to look at them. You can mark them --
MR. TRISCHLER: Right. I understand that. I understand, but it's a nice handy

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reference of what the contents of his file were, so I was going to mark them as a numbered exhibit, if that's okay.
MR. SLATER: Well, yeah, I'm not going to tell you that's all the materials in his file, though, because I don't know that it is. I don't think it is. I don't think we printed everything. So I don't think that's going to -- his file is -- I mean, you have everything. I just can't tell you those table of contents is everything because I don't think we sent him everything.
MR. TRISCHLER: Fair enough.
(Whereupon, Exhibit 20 was marked for identification.)
BY MR. TRISCHLER:
Q. Dr. Hecht, I'm just trying to -- what I'm obviously interested is in knowing everything you may have read, reviewed and relied upon.
Do you have the tables of contents for the binders in front of you?
A. Yes.
Q. Can you take a look at those and tell me whether those tables of contents contain the documents and literature that you relied upon?

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MR. SLATER: I'm sorry, Clem. You're asking him to do it? He's going to have to sit there and walk through it, compare it to the "Materials Reviewed" list and his whole report? Is that what you're asking him to do?
MR. TRISCHLER: I don't really want him to do that, Adam --
MR. SLATER: But, I mean, you have it attached to the report, you have the references in the report, so you can mark the tables of contents, you can do whatever you want, I'm just not really sure what we're getting at. You have the tables of contents. Is there something on those tables of contents that you think wasn't in the report? You can tell us and ask him the question, but I don't think so.
MR. TRISCHLER: I guess that's the question. Let me ask that question.
Q. Do you know if there's anything listed on the tables of contents in these binders that were not cited in your report?
MR. SLATER: You want him -- you want him to go through and compare everything? I

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mean, I'm told by Chris that he thinks that the tables of contents are pretty comprehensive, if not everything. But I just can't swear to it right now. Short of him comparing everything, how else is he going to be sure?

MR. TRISCHLER: I didn't get the binders until yesterday. I didn't get a chance to look at them. I'm just trying --

MR. SLATER: Clem, we gave those binders as a courtesy because they're not new materials. They're all things you already had.

MR. TRISCHLER: And I'm not complaining, Adam. I'm trying to figure out whether there's anything on here that I haven't seen or hasn't been identified before. I don't think that's an improper question.

MR. SLATER: No, but I'm saying wouldn't it be easier to have someone in your office go down the list and compare to the report and see if there's anything new?

MR. TRISCHLER: Well, perhaps, but I wasn't smart enough to do that.

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MR. SLATER: That's not -- I'm not being nasty, so I don't need that comment.

MR. TRISCHLER: I didn't suggest you were being nasty.

MR. SLATER: Look, you use the time any way you want.

Do you know yet if anyone else plans to follow up after you because we are probably at seven hours now?

MR. TRISCHLER: I don't how long we're into it and I don't know the answer to that question, but let's just see if we could get this done and then we'll move on to something else.

THE VIDEOGRAPHER: Counsel, sorry to cut it. Just to let you know, I don't have a document, the table of contents --

MR. TRISCHLER: I know you don't. I already said that you don't have it.

THE VIDEOGRAPHER: I'm saying if you want to send it to me later on, I can mark that as the next exhibit.

MR. TRISCHLER: Right.

THE VIDEOGRAPHER: And we have about seven minutes on this media, just so you

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know.

Thank you.

BY MR. TRISCHLER:

Q. Do you know offhand, Doctor -- and I don't know how much time you spent with the binder -- do you know offhand whether there's anything in the binders that is not identified in the documents reviewed that we marked as the last exhibit and the references that are mentioned in the report?

A. No. I mean, offhand, you know, the binders contain what's in the report.

Q. Is there any work that you've done since preparing your report in this case?

A. What do you mean by work?

Q. Well, I mean --

A. I had to review all of the material. I mean, that's work.

Q. Sure. Fair enough.

Other than reviewing the material, is there any new work that you did, any new studies that you looked at, any additional research that you've done since you wrote this report in July?

A. No. Not relevant to this case.

Q. As part of your work in this case,

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have you reviewed the reports of other experts that were retained by the plaintiffs in this litigation?

A. No, not the reports. I did see some transcripts of, you know, parts of testimony, but not -- I didn't review the report, I haven't reviewed any of the reports.

Q. I'll represent to you that the depositions of the experts for the plaintiff are only taking place recently, so that's including your deposition obviously.

I'm looking at the list of deposition testimony that you reviewed that's part of our last numbered exhibit and --

A. No, I didn't review those. I don't know why that's there. I haven't seen them. I haven't seen those.

MR. SLATER: Dr. Hecht, can you wait until he asks you a question, please? He hasn't asked you yet. He's moved off the expert reports. He's onto something new now.

Q. You've not reviewed any expert reports from any other expert in the case; true?

A. No. True.

Q. You've not seen any of the deposition

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transcripts from any of the experts in the case?
A. Correct.
Q. You've not spoken to any of the other experts retained by plaintiff?
A. Correct.
Q. And I take it that you're not relying upon any other expert retained by plaintiff to support any of your opinions in this case?
A. Correct.
Q. I asked you before about medical records and you told me you haven't reviewed any patient medical records.
Have you reviewed any pathology slides or tissue samples for any plaintiff?
A. No.
Q. Have you reviewed any of the reports of any of the defense experts in this case?
A. No.
Q. Do you know who any of the defense experts are?
A. No, I do not.
Q. When's the last time you gave a deposition or sworn testimony under oath?
A. Repeat the question, please. I didn't hear the whole thing.

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Q. Sure.
When's the last time you gave a deposition or other sworn testimony under oath?
A. I don't remember the exact date, but I believe it was about ten years ago in a case involving smokeless tobacco and cancer. I'm not sure of the exact date.
Q. Were you working as an expert witness in this case ten years ago?
A. Yes.
Q. In connection with your expert work where you've been asked to give depositions or give deposition testimony, has all of it been in cases involving tobacco?
A. Yes.
Q. I guess another way of asking the same question, just to make sure I understand and get the complete answer, have you ever been involved in a litigation matter as an expert witness that did not involve tobacco?
A. No.
Q. Have you ever testified at trial as an expert witness?
A. No. No.
MR. TRISCHLER: This would be a good

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time for me to go into another area and I'm getting near completion.
Can we take a five-minute break, Adam, and if you want, I can roundtable with my colleagues and see who we have as questioning and how much?
MR. SLATER: Okay. Obviously with the caution that there shouldn't be any duplicative questioning obviously.
That's not for your benefit --
MR. TRISCHLER: I don't think any that's the intent of anybody, but I understand your position.
Why don't we take ten minutes? It'll give me a chance to look at the rest of what I want to do and then I can get some -- at least some electronic feedback from our side as to what else people think.
Okay?
MR. SLATER: Sounds good.
THE VIDEOGRAPHER: The time is 4:27. This concludes media four.
(Recess taken)
THE VIDEOGRAPHER: The time is now 4:38.

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This begins media five.
You may proceed.
Q. Dr. Hecht, are you familiar with the Pottegård study?
A. Pottegård?
MR. SLATER: Which study did you say, Clem? I missed that.
MR. TRISCHLER: Pottegård.
A. I am.
Q. I'll give you a second to grab whatever you're looking for. Are you pulling up a copy of the study?
A. Yeah, I am.
Okay. That's the Danish --
(Whereupon, Exhibit 21 was marked for identification.)
Q. Right. Yes, sir. We'll mark the Pottegård study as the next numbered exhibit. You don't have to show it. The witness has it in front of him.
In this Pottegård paper, the authors followed about 5,150 Danish patients who used valsartan, correct?
A. Yes.
Q. And I think what the paper tells us

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is that the scientists who did this study followed these individuals for a median of 4.6 years and examined cancer rates in valsartan users as compared to a cohort of non-valsartan users, right?
A. Yes.
Q. Based on your review of this study, was it a good, well-designed study?
A. Well, you know, the follow up -- the sample size was pretty small and the follow up is also pretty small. So I mean as an initial pass at the problem, and, you know, the effects of the NDMA in tablets, I guess it was okay. But, I mean, it's a relatively small study and the follow up is not very long, so it's not too surprising that it didn't find anything. So, you know, a negative study doesn't really prove anything.
Q. So as with all studies, there were some limitations to it?
A. I wouldn't say all studies. That's a very broad statement.
Q. I thought you said that all studies have limitations?
A. Maybe I said that, but not all studies. Well, all studies have some limitations.

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I guess that's true. It's a very broad statement.
We do experimental studies here that I don't really think have any limitations. When you're talking about studies of populations, then the limitations become more -- there can be more limitations.
Q. In any event, what Pottegård reported was that there was no evidence of a markedly increased short term overall risk of cancer from the valsartan containing NDMA, correct?
A. Yes.
Q. You cite Pottegård in your report that you prepared for this case, right?
A. Yes.
Q. And when you prepared this report back in July, did you understand that it was going to be filed with the Federal MDL Court?
A. Federal MDL Court is what?
Q. That's the court --
A. I don't think so. I'm not sure I know what you're talking about.
Q. I'm trying to tell you, explain it to you.
It's the court where this litigation is based. Did you understand that this report was

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going to be filed with the court?
A. Yes.
Q. And did you put together the report as a summary of the scientific basis for the opinions that you were offering?
A. Yes.
Q. Do you agree that a report of this nature should not misstate or misrepresent the state of clients as reflected in the literature?
A. Yes.
Q. I assume you'd agree with me that scientists are not supposed to take liberties in preparing reports of this nature, correct?
A. I don't know what you mean by "take liberties."
Q. Well, stretching the truth or distorting findings is not what a scientist is supposed to do.
Can we agree on that?
A. We never stretch the truth or distort findings.
Q. And so when you cite to Pottegård in your report -- strike that.
When you put this report together, you already told me that one of the questions that

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was at the heart of this was whether or not NDMA can cause cancer in humans, correct?
A. Yes.
Q. So when you cite to -- here, we have a study like Pottegård that aims to answer that very question, right?
A. Yes.
Q. When you cite to Pottegård in your report, you make no mention at all of the authors' conclusion that NDMA in valsartan was not found to increase the short term overall risk of cancer?
A. No.
Q. Right? Never mention that?
MR. SLATER: Objection.
You can answer.
A. That's what you say.
Q. Well, it's what I say, but it's truthful, right? You never mention it in your report --
A. Okay.
Q. -- what Pottegård included?
A. All right. That's an oversight. I should have mentioned it.
Q. Because that's an important observation obviously, right?

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MR. SLATER: Objection.
A. It's a preliminary observation. I don't know if it's really an important observation.
Q. It's something an objective scientist would want to disclose, don't you think?
MR. SLATER: Objection.
Wait. Time out, Dr. Hecht.
Objection.
Argumentative.
Do you have a question, rather than just making statements at the witness?
MR. TRISCHLER: I just asked it and he just answered it.
MR. SLATER: Yeah, but you didn't ask. You're just throwing statements at him instead of asking the question.
Do you have a question about Pottegård? Do you have a question about something?
MR. TRISCHLER: I have another one that I'll ask as soon as you're done.
BY MR. TRISCHLER:
Q. Why did you omit Pottegård's conclusion that there was no short term overall

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risk of cancer associated with the use of valsartan with NDMA from your report?
MR. SLATER: Objection to the terminology and foundation.
You can answer.
A. I guess I have to find the page where the --
Q. Sure. I can help you --
A. -- Pottegård is discussed, so I see exactly what I said here. What page is it?
Q. Page 16 is where I see it, both in the first full paragraph and the last.
A. Yeah, I summarize the EMA comments. EMA statement cites and discusses a study performed in Denmark. That's the Pottegård study.
I'm a little confused here. Yeah.
So what's your question? What is your question?
Q. Why did you make no mention of Pottegård's conclusion that NDMA in valsartan did not lead to an increased short term overall risk of cancer?
A. Well, I guess I took the NDMA valuation of the 4.6 year follow-up interval was likely too short, so I didn't discuss it further than that. I might have -- might have discussed

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it more.
Q. Well, what you did cite to with respect to Pottegård was you make a suggestion at page 16 that the study found an increased risk for colorectal cancer and uterine cancer.
Do you see that at page 16?
A. Yes, I see that.
MR. SLATER: That's the only question, Doctor. Did you --
A. I'm a little puzzled by that.
Q. Is that an accurate statement? Is that what Pottegård actually found?
A. In the analysis of single cancer outcomes, increased risks were seen for colorectal cancer and for uterine cancer, although neither these, nor other single cancer outcomes reached statistical significance.
So yeah, that was the outcome. It wasn't -- so it's -- it's not exactly right, what's written here. It's a little unclear. It's not that clear.
Q. "Not exactly right" --
A. I should have -- I should have -- I should have been more clear in the way I wrote this.

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Q. "Not exactly right" is a kind way of saying what you wrote is incorrect?
MR. SLATER: Objection.
Q. If you look at the results on the first page of the study, what Pottegård wrote was that the confidence intervals for the single outcome cancers were so wide as to include the null, so no conclusions could be drawn, right?
A. Yes.
Q. Looking at it now, what we can say is that Pottegård never found a statistically significant increased risk of colorectal cancer, did he?
A. No.
Q. He never found a statistically significant increased risk of uterine cancer, did he?
A. That's correct.
Q. Those are obviously important observations that were never mentioned in your report either, correct?
MR. SLATER: Objection.
You can answer.
A. It's an oversight that should have been mentioned.

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Q. You also cite to the Gomm study in your report on page 16, right?
A. Yes.
Q. Do you have that with you, sir, and available to you?
A. I do.
MR. TRISCHLER: We'll mark the Gomm study the next numbered exhibit.
Bill, you do not have to display it since the witness has it in front of him.
(Whereupon, Exhibit 22 was marked for identification.)
Q. Doctor, Gomm was a study where they used the German registry database to look at over 750,000 individuals who filled valsartan scripts, right?
A. Yes.
Q. And the incidence of cancer was compared to non-valsartan users, right?
A. Yes.
Q. And we talked about how most every study has limits and I assume Gomm is no exception, right?
A. Sure.
Q. But not withstanding those limits,

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did you find Gomm to be a good study?
A. I found out to be remarkable in the sense that they sought excessive liver cancer.
Q. Did you find the conclusions in this study reliable?
A. Yes, but it needs confirmation.
Q. Gomm reached the same conclusion as Pottegård. In a national study, there was no evidence of an increase in the overall risk of cancer amongst valsartan users, correct?
A. Overall, yeah. But they did find a risk -- an increased risk of liver cancer.
Q. We'll talk about that in a minute.
In terms of the overall risk of cancer, Gomm found no evidence of such an increased risk; true?
A. Correct.
Q. The conclusion is Pottegård, correct?
A. Yes.
Q. So we have two national studies done by two different groups of scientists, both concluding that NDMA in valsartan did not lead to an increased overall risk of cancer; true?
A. Well, I think the follow up would have to be much longer. You know, these are

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both -- really, they're both preliminary studies. The follow up would have to be longer and we would need to know more about who actually took which pills, which is not addressed here.
So, you know, these are -- I think these are okay as preliminary studies, but I think they're both preliminary. We need -- we would need a -- more of a follow up, for example, you wouldn't really necessarily expect to see an increase in liver cancer within three years.
And the same goes for the other study. I think the follow-up time is too short and there are many -- there's many questions about both of these studies.
Q. All right.
Limitations aside, you would agree with me we do have two nationwide studies which both reported no increase in the overall risk of cancer.
Agreed?
A. Yes, but I wouldn't put the limitations aside. Limitations are there. It's obvious what they are.
Q. In your report --
A. I don't think you would expect an

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increased incidence of liver cancer within three years.
Q. In your report to this court where you tried to honestly and objectively answer the causation question, you never mentioned the findings of either one of these studies, right?
MR. SLATER: Objection.
A. No, they're both in the report.
Q. No, they're not. We went through it. You don't mention --
MR. SLATER: Counselor, lower your voice towards the witness and look at the page because he just told you it's in the report. You obviously haven't read page 16.
You're not going to attack him aggressively like this. You're not going to do it. You're just not going to do it.
Q. Sir, do you ever mention in your report that Pottegård found no overall increased risk of cancer? Yes or no?
MR. SLATER: Objection.
We went through this already.
You can answer again.
A. Pottegård? We already went through this. Pottegård did not find a significant

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increase.
Q. Correct.
Am I correct --
A. Did not find -- did not find a significant increase.
Q. Correct.
My question is did you ever mention that in your report?
MR. SLATER: Didn't we go through that already --
A. We already did that. I already told you that was an oversight. It's unclear the way it's written. I already told you that. I already told you that.
Q. Gomm found no --
A. You know, none of us are perfect. Sometimes we make mistakes.
Q. I understand.
A. Maybe even you do.
MR. SLATER: Doctor, it's okay.
Q. Gomm found no overall increased risk of cancer.
Did you ever mention that fact in your report?
A. No.

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MR. SLATER: Take your time, please.
A. The Gomm paper found an increased risk for liver cancer was identified, but no association was identified for the overall risk of cancer. So yeah, it's in there. It's in there.
Q. All right.
You've talked about what Gomm observed with respect to liver cancer.
Do you understand that valsartan is a long-term-use medication?
A. Yes.
Q. Patients that are taking ARBs to control hypertension don't use these medications acutely, right?
A. Right.
Q. When they take valsartan or any ARB, the patients tend to be on them for years, correct?
A. Yes.
Q. In Gomm, when the authors adjusted for long-term use, isn't it true that the data could no longer find an association for liver cancer?
MR. SLATER: Objection.
You can answer.

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A. I don't know. I'd have to -- I have to look at it again. I'm sorry.
Q. Sure.
If you have to study in front of you, you might want to take a look at page 358.
A. Yes. No dose-dependent effect on the risk of liver cancer was found for higher exposure, bearing lag times of six month to two years, also did not alter the effect. Valuation three year long-term use resulted in decreased sample size and showed no significant association with liver cancer. So that was 1.22, but it was not significant.
So yeah, that's what they found. But I mean I really think both of these studies are somewhat flawed. That's my opinion. Because with a low-dose dimethylnitrosamine in animals, it takes time for the tumors to appear. You wouldn't get them in the same kind of time scale they're talking about here. Humans are far more susceptible to liver cancer based on exposure to dimethylnitrosamine than animals --
Q. What's the --
A. -- or the -- you know, the timeframe I simply think is not long enough. Even in

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tobacco and cancer, where you have a much stronger carcinogen, the timeframe is minimum of 20 years.
Q. And that's a minimum of 20 years from exposure to the carcinogen to the development of the tumor?
A. Right.
Q. So, you know, anyone suggesting that they got a tumor from valsartan-containing medication that developed in a year or 18 months, that would be highly unlikely because the time period is just too short?
MR. SLATER: Objection.
You can answer.
A. I don't know about anyone -- okay? -- because, you know, there could be predisposing conditions. It could be that the person had other exposures. So I wouldn't say anyone. But in general, you would expect that the timeframe would be longer than three years.
Q. You expect the timeframe to be more along the lines of ten to 15 years at least, right?
A. That's what you would expect, but you know, it could be that there's something about NDMA that we don't really know about.

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Q. It sounds like there's a lot we don't know about NDMA.
MR. SLATER: Objection.
A. No, I wouldn't say that. I wouldn't say that at all. We know a lot about NDMA. We know a lot about it.
Q. Well, it sounds like you didn't hear my question, so let me ask --
MR. SLATER: It wasn't a question --
A. There might be a co-factor involved in these patients. Maybe high blood pressure or hypertension previously unrecognized that shortens the waiting period.
Q. Have you ever seen --
A. No, we don't know.
Q. Have you ever seen a study suggesting that hypertension shortens the latency period for tumor development?
A. No, I haven't seen it.
Q. So we were talking about Gomm and I was on page 61 and Gomm provides a table regarding the authors' evaluation of single cancer outcomes.
Do you see that?
A. Yes.
Q. And Gomm found no statistically

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significant association between bladder cancer and NDMA in valsartan, right?
A. No. I don't see bladder cancer. You're looking at table two?
Q. No. Table three on page --
A. All right. Sorry. Yeah, right. Right. They didn't --
Q. Let me ask the question, please.
Gomm found no statistically significant association between bladder cancer and NDMA in valsartan, correct?
A. Yes, correct.
Q. No statistically significant association between breast cancer and NDMA in valsartan, correct?
A. Correct.
Q. No statistically significant association between colorectal cancer and NDMA in valsartan, correct?
A. Correct.
Q. No statistically significant association between kidney cancer and NDMA in valsartan, correct?
A. Correct.
Q. No statistically significant

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association between lung cancer and NDMA in valsartan, correct?
A. That's correct. But I wonder if these were all nonsmokers. I don't know if that's the case.
Q. No statistically significant association between pancreatic cancer and NDMA in valsartan, correct?
A. Correct. Well, malignant melanoma.
Q. No statistically significant association between prostate cancer and NDMA in valsartan, correct?
A. Correct.
Q. No statistically significant association between uterine cancer and NDMA in valsartan?
A. Right.
Q. Do you agree that the metabolism of NDMA and NDEA is the only mechanism by which these substances could possibly cause a mutation?
A. Yes.
Q. So NDMA and NDEA could circulate in the body and unless and until they become metabolized, they'll just be excreted without causing harm, right?

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A. Say that again, please.
Q. Absent -- what I was saying was until NDMA and NDEA become metabolized, they would simply be excreted from the body without causing harm?
A. That's true, but, in fact, you see very little excretion of unchanged NDMA in the urine. When it's taken orally, it's metabolized very effectively by the liver and other tissues.
Q. Does most of the metabolism of the NDMA occur in the liver?
A. As far as we know, yes.
Q. And at this point in time, would you say that the scientific community has good data on the metabolism of NDMA and NDEA in the human body?
A. Yes.
Q. Do you agree then that the primary metabolism of NDMA and NDEA takes place through the cytochrome P450 enzyme?
A. Yes.
Q. And that's in the liver. That's where that enzyme is primarily located, right?
A. No. They're in other tissues also.
Q. It's not in every organ system of the body, is it?

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A. Just about.
Q. Just the enzyme?
A. Yes. There are different forms in different tissues. Not just in the liver. The lung, kidney, small intestine, esophagus, oral cavity. They all have P450 enzymes. The liver, of course, is the main metabolizing organ in the body and has a higher P450 content than other tissues, but all tissues have P450s. Different ones. There are whole books written on it.
Q. Okay. I'll take your word for it.
Does the scientific community at this point in time have a great deal of valid reliable data about the type of DNA damage caused by NDMA and NDEA?
A. Yes.
Q. Have you ever stated that there are ways to look at a DNA adduct formation and how much damage comes from nitrosamine exposure but right now, in 2021, we don't have that type of data?
A. I'm not sure I understand your question.
Q. My question is simply have you ever made the statement that "We do not have the data

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in 2021 to evaluate the type of DNA damage caused by nitrosamines"?
A. I don't think I ever made that statement, no. We have a lot of data. We have a huge amount of data.
Q. Who is Joseph Guttenplan, G-U-T-T-E-N-P-L-A-N?
A. Guttenplan.
Q. Sorry for the mispronunciation.
Who is Joseph Guttenplan?
A. He's a scientist at New York University.
Q. Is he an expert in the field of chemical drug and genetic drug toxicology?
A. Yes.
Q. Was Dr. Guttenplan part of the FDA workshop that took place in March?
A. Yes, he was there.
Q. During that workshop was one of the issues that was discussed the body's DNA repair mechanisms?
A. Yes.
Q. In that workshop, was it discussed among the experts and agreed that the small amounts of nitrosamines in medication were sub

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threshold with respect to the body's DNA repair abilities?
A. May have been discussed, but I don't recall that that conclusion was made.
Q. Did Dr. Guttenplan observe that the nitrosamine levels in medicines were so low that they were not approaching threshold for enzyme saturation? Do you remember that comment or observation being made?
A. For which enzyme? Repair enzymes, you mean?
Q. Yes, sir.
A. I don't follow what you mean.
Q. My question was did Dr. Guttenplan state at the FDA workshop that the levels of nitrosamines in medicines were so low that they were not approaching thresholds for enzyme saturation in the body?
A. You're still not clear. First, you were talking about DNA repair enzymes and then you're talking about nitrosamine metabolizing enzymes, so I'm not sure which ones you're actually referring to.
Q. When Dr. Guttenplan used the term "sub threshold," what did you understand that to

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mean?
A. I believe -- I believe he's talking about with respect to the nitrosamine-metabolizing enzyme, like 452E1 and others that are in the body, that those enzymes are not saturated by the kind of exposure that you would get from valsartan.
Q. When those enzymes are not saturated, what that means is that our body has the ability to deal with those small levels of carcinogens, correct?
A. Deal with them, yes. In dealing with them, it creates a DNA damaging agent. That metabolism is absolutely required for NDMA to cause liver cancer.
Q. Who is Dr. Richard Adamson?
A. He's a consultant now. He's a former director of the Division of Cancer Etiology at the National Cancer Institute, which is the US -- main US governing body that does research on cancer.
Q. Was Dr. Adamson also at the workshop in March?
A. Yes.
Q. Do you recall Dr. Adamson also discussing the issue of the body's DNA repair

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mechanisms and whether low levels of NDMA or NDEA in drug products was expected to present a significant risk of harm to the patient population?
A. I don't recall his exact comments, but he's certainly an expert. He has done studies exposing primates to NDEA.
Q. Isn't it true that Dr. Adamson stated that the low levels of nitrosamines in the drugs were so low that he would not expect any long-term risk of patient health since there was no saturation or competition for activation of the body's repair enzymes at those levels?
A. Are you quoting?
Q. I'm asking if that's what you heard him say.
A. I don't remember if that's what I heard him say. I'm asking you whether you're quoting from the transcript. In that case, it's true.
Q. So is that statement correct, that low levels of exposure to nitrosamines would not be expected to cause long-term harm to the patient population because those levels would not be expected to saturate or compete for activation of

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the body's repair enzymes?
MR. SLATER: Objection.
Lack of foundation. Multiple --
A. It's totally confusing, what you're saying. Okay? The low levels would be very effectively metabolized by the P450s in the liver and other tissues of the body, leading to the formation of highly reactive DNA damaging intermediates that cause mutations in DNA. Some of those may be repaired by a repair enzyme such as MGMT and I think what you're saying is that the MGMT activity would not be saturated. I think that's what you're referring to, but the way you're saying is it very confusing. Really muddies the water.
The bottom line is that your body definitely has the ability to convert the NDMA in valsartan to a DNA methylating agent that's going to form O6-methylguanine. I can tell you with 100% certainty that a person who takes a tablet of valsartan that's contaminated with dimethylnitrosamine will form a finite amount of O6-methylguanine in their DNA. Some of that may be repaired. Some of it may lead to mutations.
Q. My question was at the FDA workshop

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in March, was it the conclusion of the scholars that were impaneled by FDA that the levels in this case were so low that there was not expected to be a significant risk to public health because the body's repair mechanisms would allow for or prevent the development of mutations?
A. Yes, that was the conclusion.
Q. I guess --
MR. SLATER: Objection.
A. What?
Q. I guess then what I'd like to ask you is this --
A. Are you quoting? I mean, were you quoting from the report?
MR. SLATER: Doctor, if you want to see the transcripts, you could ask him to show it to you.
Q. I'm just asking you a question.
A. I'm just asking you whether you're quoting from the report or not.
Q. I asked you if that was a conclusion of the panelists.
A. I don't remember. I mean, you have the report right in front of you, so why don't you tell me?

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Q. We know that you've done research on NNN and NNK in your career and we know that both of those are known Class 1 carcinogens in tobacco, right?
A. Correct.
Q. We know that tobacco also is laced with other carcinogens, not just those two tobacco nitrosamines, right?
A. Tobacco smoked, yes. Unburnt tobacco is another story.
Q. I've been led to believe -- and I don't know whether it's true or not -- is that tobacco contained over 70 carcinogens.
Is that the case?
A. Tobacco smoke, yes.
Q. I think that you have written that cigarette smoking causes up to 90% of all the lung cancers in the world and is the largest cause of cancer death in the world, yet only ten to 20% of lifetime smokers will get lung cancer?
A. Correct. It's no longer the largest cause of cancer in women in the world. That's breast cancer. But everything else you said is correct.
Q. All right.

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We talked earlier about the Gushgari paper that told us that the estimate is that smoking leads to the injection of 25,000 nanograms of nitrosamines per day.
Do you remember that?
A. Yes.
Q. And I assume that doesn't need -- that's not even taking into account then the other carcinogens contained in tobacco smoke, right?
A. Correct.
Q. So if only ten to 20% of individuals exposed to 25,000 nanograms a day of nitrosamines plus other carcinogens acquire lung cancer after a lifetime of smoking, do you have any estimate or are you capable of providing an estimate as to the percentage of valsartan users that you would expect to develop cancer from a less-than-lifetime exposure to nitrosamines?
A. I'm not capable of making that calculation, but presumably the risk would be less than from smoking.
Q. Do you know what the --
A. I cannot make that calculation.
Q. Okay. Fair enough.
Do you know what the background rate

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of cancer in the US population is?
A. What do you mean by background rate?
Q. How many people will get cancer in one form or another in their lifetime?
A. Yes. I know that number, but I'm afraid I can't quote it off the top of my head. But that number is certainly available.
Q. Okay.
Do you know what the background rate of cancer among Americans over the age of 50 who suffer from hypertension might be?
A. Not offhand.
Q. Are you able --
A. I don't know what you mean by background.
Q. Maybe --
A. What does background mean?
Q. Maybe it's just my poor language.
I'm just trying to tell, you know, how many -- what percentage of Americans over the age of 50 who have hypertension will develop cancer?
A. I can't answer that offhand. It's definitely available.
Q. I'm only asking --

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A. Definitely available.
Q. I understand. I'm only asking --
A. I can't keep all those figures in my brain.
Q. I'm just asking what you know. If you don't know, just tell me you don't know.
Do you intend to present this court with any statistical or epidemiological evidence to say that there will be a statistically significant increased rate of cancer above the background rate simply because of a less-than-lifetime increase in the intake of NDMA when all of the individual plaintiffs have already been exposed to nitrosamines exogenously every day of their life?
MR. SLATER: Objection.
You can answer.
A. First of all, your question doesn't make a lot of sense the way --
Q. Well, which part doesn't --
A. The way that all the people have been exposed to nitrosamines every day of their life. That's incredibly nonquantitative. I mean, I could never agree with a statement like that.
In any case, I'm not intending to

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make any numerical estimates because that's not what I do. That's for the risk assessors to do.
Q. That's fine. This is what I'm just trying to find out. Let's just assume hypothetically that those readily-available statistics you talk about tell us that 30% of people over the age of 50 who have hypertension will develop cancer in one form or another.
Okay?
A. Okay.
Q. And you just accept that number --
A. Okay.
Q. -- for the purpose of my question.
A. Right.
Q. What I'm trying to figure out is are you going to offer an opinion that that population subgroup is at some statistical increased risk of cancer just because they received a less-than-lifetime increase in the intake of NDEA or NDMA for some period of time?
A. Yes. I would be comfortable with offering an opinion, but not necessarily making a calculation.
Q. Well, that was my question.
What is the -- what is that increased

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risk? Can you calculate it or estimate it?
A. No, I can't. I can't do that.
That's not what I do.
Q. That would be the same thing for -- I think I --
A. For both.
Q. That would be the case for both NDMA and NDEA --
A. That's for the risk assessor to do.
Like EMA and any others.
MR. TRISCHLER: I think I'm ready to pass the witness.
I think the information that I received, Adam, is that there are others who have -- a few others that have questions, maybe one or two on the side, but I'll let them speak for themselves and I don't know if that's been updated since I finished. So -- but I think --
MR. SLATER: Whoever it is needs to identify themselves and I'm going to object to and expect that there will not be any questioning that's going to go into the areas that Mr. Trischler covered.
It's hard for me to imagine there is

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anything new to ask, but please don't come in and make me start objecting and have a back and forth. I would appreciate that because it's been a long day and I have some questions to follow up on from Mr. Trischler's lengthy questioning.
MR. FOWLER: Good afternoon, Dr. Hecht. It's Steven Fowler with Greenberg Traurig.
I believe the remaining defendants have an hour and a half or so of questions. I've got quite a bit of questions. I assure you it's not my intent to ask any questions that Dr. Hecht has answered, but I do have questions and I'm just -- in fairness, I think it's about an hour and a half or so --
MR. SLATER: Go ahead. Start your questioning. I've heard that before.
Let's get going and we'll go question by question and see if it's new questions because it's impossible for me to imagine -- unless you guys are just going to walk the dog and come up with things to ask about that are hyper specific to a specific manufacturer just to ask questions, I feel like this has

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been a thorough deposition and we should be able to turn it over to me soon.
So go ahead. Start asking your questions, please.
MR. FOWLER: I will and I'll appreciate if you simply just object to form and --
MR. SLATER: I don't need a coaching --
MR. FOWLER: -- launching into the diatribes I've been hearing all day, so just object to form and I'll ask my questions.
MR. SLATER: Okay. Now that you you're done talking I'll respond.
Please don't coach me. Please don't tell me what to do --
MR. FOWLER: Same here.
MR. SLATER: -- but please realize that duplicative questions, you'll need to move from question to question.
You may proceed.
MR. FOWLER: What I'd like to do first -- good afternoon, Dr. Hecht. My name is Steve Fowler on behalf of the Teva defendants.

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What I'd like to do first is actually mark as the next exhibit your Notice of Deposition today. I don't think that that's been marked.
Can we get that marked --
MR. SLATER: You're going to need to do that yourself, sir. You're going to have to have someone put it up.
MR. FOWLER: Adam, I'm not talking to you.
Steve, are you able to share the screen? We have three Steves on the line.
THE VIDEOGRAPHER: Do you have somebody else who is going to be displaying?
MR. FOWLER: The exhibit was just introduced and it can be displayed by the concierge as I understand.
THE VIDEOGRAPHER: As far as the record, it will be Exhibit 23.
(Whereupon, Exhibit 23 was marked for identification.)
MR. FOWLER: Is it going to be displayed or am I going to --
MR. SLATER: It's on the screen.

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EXAMINATION BY
MR. FOWLER:
Q. Doctor, have you seen this document before?
A. No.
Q. I would submit this is the notice for you today and if we can go to page three of the notice, you'll see that we've asked for certain items to be brought with you and that would include any sort of files or records that you have with regard to this subject matter.
And Dr. Hecht, I heard today you've spent much of your career on nitrosamines and my question to you is do you have a file that you've maintained on nitrosamines and the risk of carcinogenicity?
A. A file on risk of carcinogenicity in humans? In animals?
Q. Let me break it down.
Do you have a file on nitrosamines, Doctor?
A. A file? Everything is summarized in my publications. I mean, I do not have all of the original records from the research that we've done. I have files and --

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Q. Do you maintain any -- setting aside this litigation, Doctor, do you maintain a file on nitrosamine as being an area of your research we've heard about today?
A. Yes, I do. Yes.
Q. And do you maintain that with paper copies of journal articles you may have printed over the years?
A. Yes. I have several file cabinets, but, you know, in the last, I don't know, eight years or so, everything is online.
Q. Is your file on nitrosamines organized at all by particular nitrosamines such as NDMA or NDEA?
A. No.
Q. When you were asked to participate in the FDA panel, did you undertake any preparation for that panel? Did you undertake any research before you appeared?
A. No.
Q. With you today, Doctor, do you have any -- let me ask you this: I've seen you pick up the red book a couple times.
What else do you have in your space there at your office? Can you hold it up? Do you

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have binders? What do you have, sir?
A. In my office?
MR. SLATER: Dr. Hecht, one second. This was covered extensively earlier.
MR. FOWLER: It wasn't. I've seen him picking up things and looking at things. I just want to know what else he's got.
THE WITNESS: You want me to answer him?
MR. SLATER: Yeah, go ahead, answer him.
We've moving quickly towards concluding his questioning if this is --
A. I have binders that have the publications and the other data that was mentioned in the written document and I have some of my books that I refer to, including, you know, the IARC 1978 valuation. I have all of the IARC monographs up until about year 2000 or maybe a little later. They're not all here in my office anyhow.
Q. Thank you, sir.
A. Does that answer your question?
Q. I believe so, sir. Thank you.
Doctor, when evaluating the issue

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before you, which I think we've acknowledged is whether the level of NDMA and NDEA found in the valsartan products increases the risk of carcinogenicity, did you apply a specific level of -- let's start with NDMA -- in your analysis as it pertains to the valsartan products?
MR. SLATER: Objection.
You can answer.
A. No. I mean, I did not do a risk assessment.
Q. Am I correct you were --
A. That was done by others.
Q. You were attempting to evaluate whether or not the levels of NDMA and NDEA in the valsartan tablets poses an increased risk. Wasn't that what the question you were answering? I thought we heard that earlier.
MR. SLATER: Objection.
Asked and answered.
You can answer.
A. I don't know what you mean by increased risk. Sure, there's an increase in risk. No doubt about it. It shouldn't be there. The amount should be zero, but I didn't -- I did not do the formal risk assessment. Those were

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done by FDA and EMA, among others.
Q. What level --
A. And I don't do it. That's not what I do.
Q. I understand, Doctor.
What level of NDMA are you operating from when evaluating the valsartan?
A. Zero.
Q. Doctor, you understand FDA has found --
A. It should be zero.
Q. Doctor, that's a liability --
A. It should be zero.
Q. This can take a while.
A. The amounts that have been found in the API from ZHP ranged from about ten to 120 parts per million, I believe.
Q. Do you believe that the levels in the API is the same as the levels of NDMA in finished dose valsartan products?
A. No. No. It would be -- it would be higher than the API for finished products.
Q. Right.
So we're only here today about the finished dose products that plaintiffs allegedly

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consumed and my question is simply this --
MR. SLATER: You know what, counsel? Before you ask a question, we're taking a break.
MR. FOWLER: Don't talk over me.
MR. SLATER: We're taking a break. We've been going over an hour again. It's 5:30 on the east coast, it's 4:30 -- the doctor has been going for now eight-and-a-half hours, so we're going to take a break.
MR. FOWLER: I was in the middle of a question --
MR. SLATER: I stopped you before you asked it, you talked over me. We're going to take a break for ten minutes.
MR. FOWLER: Okay.
Thank you, Doctor. We will take a break.
THE VIDEOGRAPHER: Time is 5:34. This concludes media five.
(Recess taken)
THE VIDEOGRAPHER: The time is now 5:49.
This begins media six.

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You may proceed.
Q. Doctor, what I was trying to get at earlier is simply this question: Do you think and agree that it's reasonable for those scientists who are evaluating the risk, if any, from the levels of NDMA and NDEA in the valsartan to use the geometric mean value of all of the levels FDA measured in a particular dose of valsartan?
MR. SLATER: Objection.
I don't understand.
THE WITNESS: Do you want me to answer that now?
MR. SLATER: If you can --
A. Were you going to reply to his objection first?
Q. I have no reason to.
Go ahead, Doctor, if you do understand the question.
A. Could you repeat it again please?
Q. Yes, sir.
Do you agree it makes sense to take an average number, a geometric mean of all of the various manufacturers levels of NDMA measured by FDA in, let's say, the 320 milligram dose of valsartan when evaluating what, if any, risk

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exists from that level of NDMA?
Do you understand that?
A. Yeah. You want to take the geometric mean from all of the manufacturers. I'm not sure that really makes sense because the different manufacturers may have different amounts.
Q. For example, you would not expect any single patient to have taken the highest level of NDMA detected in the 320 milligram valsartan for the period at issue, would you?
MR. SLATER: Objection.
A. I wouldn't know. I have no idea.
Q. So do you think it's unreasonable to take an average number of all of the manufacturers of the affected valsartan when evaluating the risk?
MR. SLATER: Objection.
You can answer again.
A. I really don't know. I mean, an average would be the place to start, I suppose.
Q. Okay.
A. You know, one would have to be mindful also of the high doses because the high doses are where you more likely see an effect. So it might make sense to evaluate the high doses

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first, you know, above, let's say, the 80th percentile, something like that. And you know, if you didn't find an effect there, then you could probably safely conclude that there would be no effect to the lower doses.

So I'm not sure that the geometric mean is necessarily the way to go about this. As I mentioned, I'm not the risk assessor, so you really -- you're bringing me into an area that's not my area of expertise.

Q. Yes, sir, thank you.

And it follows from that that you made no attempt to evaluate the specific level of NDMA from any of the manufacturers' valsartan tablets that FDA measured. You didn't consider any of those specific levels in forming the opinions we see in your report; is that correct?

MR. SLATER: Objection.

A. I didn't do calculations, no.

Q. You didn't rely on any of the specific numbers that FDA measured in any of the valsartan in forming the opinions contained in your report, correct?

MR. SLATER: Objection.

Lack of foundation.

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You can answer.

A. Come back to it again. I mean, I didn't do a formal risk assessment. That's not what I do. So --

Q. I understand, Doctor.

A. -- I don't really know what you're driving at with this question. I already told you I don't do these calculations. EMA did calculations, FDA did calculations. Their results are, I think, all documented.

Q. In your research --

A. I don't really see what you're asking -- why you're asking me. I mean, ask the person at EMA who did the calculations.

Q. Thank you, Doctor.

When you've done your research on other nitrosamines and in tobacco, like the NNN and NNK, do you ever evaluate the level of NNN or NNK in writing your papers or forming your conclusions on those studies?

A. Yes, we do.

Q. The levels are important, correct?

A. Yes, they are.

Q. I think we started the day with dose and duration are a key to any evaluation.

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Do you agree with that?

A. Yes.

Q. Doctor, forgive me, I'm going to -- in an effort to be efficient, I'm going to jump around a little bit, so forgive me if they're disjointed and if you don't follow me, please let me know.

Exhibit 1 is your report. If you could please -- I'll direct your attention to page eight.

A. Okay.

Q. The last full paragraph that begins "The pharmacokinetics ..." -- are you with me, sir?

A. Yes.

Q. You state in the third line "Consistently, these studies have demonstrated high systemic clearance and high oral bioavailability of NDMA."

Do you see that?

A. Yes.

Q. The support for that statement is contained in part of that Dr. Gombar beagle study that we looked at; is that correct?

A. Yeah.

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Q. And if we could please look again at Exhibit -- at Exhibit 8, the beagle study --

THE VIDEOGRAPHER: Would you like that up on the screen, Counsel?

MR. FOWLER: Just pause on that.

I may be able to move quicker.

Q. Doctor, let me ask you do you have any understanding of the -- any differences between the metabolism of the capacity of a beagle to metabolize NDMA with the CYP2E1 enzyme compared to humans? Do you have any understanding of that?

A. I don't know if 2E1 has actually been identified in beagles. I'm not sure of that.

Q. If beagles --

A. I think Gombar's conclusions were actually a little bit different. I think, if I remember correctly, the beagle studies came to a slightly different conclusion regarding the clearance of NDMA by the liver than the other studies.

Q. Doctor, if a beagle only has a quarter of the metabolic capacity for NDMA as compared to a human, would you agree that dogs would have less capacity to clear any oral dose of NDMA?

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A. Sure. I mean, if they have less -- if they have -- if they have less of the P450 metabolizing enzymes in their liver and other tissue than humans, then they would have less capacity to clear the dose of the metabolism.
Q. Do you recall the manner of exposure in that beagle study? Do you recall whether it was by IV?
A. I think it was IV.
Q. And you agree, Doctor, with regard to metabolism, the route of exposure is essential to understanding the route of metabolism, correct?
A. Right.
Q. And the route of exposure makes a difference in the route of metabolism; true?
A. It can effect it, sure.
Q. So the metabolism that you would expect from an IV or an IP administration of a compound like NDMA, you would expect that to show different results than through an ingestion of an oral tablet containing some level of NDMA, correct?
A. Possibly.
Q. That's a medical fact, isn't it, Doctor, that if it's injected IP, it's not going

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to enter the liver through the mesentery vessels, is it?
A. Well, the distribution will be different, but ultimately, it'll be metabolized.
Q. Would it be metabolized -- it would reach organs that orally ingested via a tablet would never reach, correct, Doctor?
A. I don't know about never, but ...
Q. Okay.
Are you intending to offer an opinion as kind of set forth on Exhibit 8 that in humans that NDMA has a high systemic clearance and high oral bioavailability?
A. That's what the literature indicates.
Q. Is there any literature other than the Gombar articles on pharmacokinetics that you're relying on, sir?
A. It's been done in multiple different species pharmacokinetic studies. There's a lot of them. There's a lot of data --
Q. Yes, sir.
A. -- as stated in the report.
Q. There was a third article in the Gombar series of pharmacokinetic testing that you had in your materials.

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Correct, Dr. Hecht?
A. Say it again.
Q. There's a third article in Dr. Gombar's series, if you will, on the pharmacokinetics of N-nitrosodimethylamine.
Right?
A. Okay.
MR. FOWLER: I'd like to mark the next exhibit.
This is the Gombar article, 1990, "Interspecies scaling of pharmacokinetics of then nitrosodimethylamine."
Bear with me, Doctor.
That should pop up.
THE VIDEOGRAPHER: I'm looking for it. You didn't upload it by any chance, did you?
MR. FOWLER: I just uploaded it as Exhibit 24.
THE VIDEOGRAPHER: Excellent. Give me one moment to download it. I'm not seeing it on our Novak share file.
Did you put it on the Veritext Exhibit Share by any chance?
MR. FOWLER: Yes.

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(Whereupon, Exhibit 24 was marked for identification.)
Q. Doctor, do you happen to have a hard copy of this in your materials?
A. No.
Q. We'll do it on the screen. That's fine, sir. Okay. Thank you.
If we can please turn to the third page where it begins the discussion -- it's article page 4368. There you go.
The very first sentence of that discussion, sir, states "The role that the pharmacokinetics of a carcinogen plays its impact, both qualitatively, i.e. target organ, and quantitively, i.e. risk assessment, has not been adequately determined for most compounds assumed or suspected to be human carcinogens."
Did I read that correctly there, Doctor?
A. Yes.
Q. Do you agree that for NDMA and NDEA there has been sufficient study done to adequately understand the metabolism of those two nitrosamines?
A. There's pretty extensive data, yes.

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Q. Yes, sir.
A. I agree that it's pretty well understood.
Q. Okay.
A. There's always questions remaining.
Q. You'll see at the bottom of that that it says "The root of administration can alter the organospecificity as can" -- and it flips to the next page -- "as can manipulation of the clearance with inducers or inhibitors of metabolism."
Do you see that, sir?
A. Yes.
Q. So do you agree with that, that the route of administration can affect the organospecificity of where perhaps NDMA may land?
A. I agree with it, but if I'm not mistaken, most studies of NDMA in animals carcinogenicity studies independent of the root of administration show mainly liver cancer.
Q. Doctor, did you evaluate the animal studies with an eye towards the route of administration to assess those which best can be analogized to the oral administration through a tablet? Did you make that --
A. No, not specifically, but I know

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generally in the literature that the main target tissue of NDMA in animals -- laboratory animals -- is the liver and it's not all by oral administration.
Q. Doctor, if I use the term "downstream organs" --
A. But there are exceptions.
Q. Thank you. I'm sorry. I didn't mean to step on your response.
If I use the term "downstream organs to deliver," do you understand what I mean?
A. Yes.
Q. Okay.
Are you aware of any study that was performed on animals using oral ingestion via a tablet -- not drinking water -- via oral ingestion that demonstrated any cancers outside the liver in any oral ingestion studies?
A. Of a tablet?
Q. Or they have -- and I can't remember the name of the tool where they just put it right down the gullet, but not drinking water is my point, Doctor.
A. Yes. Oral intubation.
Q. Thank you, sir.

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Are you aware of any study that demonstrates at low doses that NDMA has caused any downstream cancer from the liver?
MR. SLATER: Objection.
You can answer.
A. Sure. It causes kidney cancer when the doses exceed a certain level that aren't metabolized by the liver when it's given orally, the doses are too high -- or not too high -- but higher doses will get kidney cancer.
Q. Yes, Doctor.
Do you agree that NDMA and NDEA are subject to first pass metabolism?
A. Yes.
Q. Have you made any attempt to determine what the saturation level is for the liver's capacity to handle first pass metabolism NDMA?
Do you understand that question?
A. In what species?
Q. Human, sir.
A. Have I made any attempt? No.
Q. Have you made any attempt using any of the animal data to understand at what level the liver's ability to fully metabolize and excrete

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the NDMA is exceeded?
A. That data is in the literature. There's plenty of data on that --
Q. Did you make any --
A. -- from the pharmacokinetic studies and even from the early studies of Magee and Swan that when the metabolic capacity of the liver is exceeded in an oral dose, then kidney tumors start to appear and there's plenty of data on that. Not only tumors, but DNA adduct studies and metabolism studies. There's a lot of data regarding the first pass clearance of NDMA given orally, a lot of data. We understand that really very well.
Q. So it follows, Doctor, that you would understand and agree with the point that NDMA will not escape the liver unless the level is at such a point that it exceeds the liver's capacity to metabolize it, correct?
A. That's what the -- that's what all the data indicates. That's correct.
Q. I'm also correct that sitting here today, you are offering no opinion as to what that level of NDMA is, correct?
A. In humans?
Q. Sir, yes.

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A. I'm not.
Q. In particular, in this case, you're not offering an opinion that the levels of NDMA and NDEA that were detected in the valsartan at issue were such that they would exceed the metabolic capacity of the liver, correct, sir?
A. I doubt that they would. I believe that they would be metabolized in the liver. That's why it was interesting to see that the study from Germany, the insurance study, showed liver cancer. But we already discussed that.
Q. And I didn't ask that part of the question, sir.
A. No, you did not.
Q. Thank you.
Doctor, do you agree that once NDMA is metabolized by the -- the PY450E1 enzyme that that metabolite is very reactive?
Do you agree with that statement?
A. One of them is, the methane diazohydroxide that everybody concentrates on because that's what damages DNA, but there's another metabolite that's formed and it's formaldehyde, which is also a carcinogen --
Q. Yes, sir, and --

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A. -- and paid much less attention to.
Q. I'm sorry.
A. Much less attention has been paid to the formaldehyde which cannot only damage DNA, but can cross link DNA.
Q. Yes, sir.
You are aware, of course, that formaldehyde is endogenously produced, correct?
A. Yes.
Q. It would be impossible for you or any other scientist to distinguish between endogenously-induced formaldehyde DNA damage from formaldehyde DNA damage as a result of NDMA metabolism, correct?
A. No. Incorrect.
Q. You can spot the difference between an endogenous formaldehyde and an NDMA formaldehyde, sir?
A. Yes.
Q. And how do you do that?
A. Well, I would have to have a label in the NDMA that people took into their bodies and then the formaldehyde that's released would be labeled and I could determine how much came from NDMA.

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Q. To your knowledge, has that study been done?
A. No.
Q. Based on --
A. In humans, it has not.
Q. Has it been done anywhere that you can point to, Doctor?
A. I don't think it's been done in animals either, but, I mean, it could be done in animals. We have looked at DNA damage from the formaldehyde produced in NDMA metabolism. We did that study. But of course in rats, you can just give NDMA and we compare to treat it with a control. The other way to do is it label NDMA.
Q. Okay.
Well, thank you for that.
But to be clear, the state of the science today, you nor anyone else can distinguish between endogenously formed formaldehyde DNA adduct and an adduct formed as a result of formaldehyde from the metabolism of NDMA; isn't that correct?
A. It hasn't been done, but it can be done. We're going to do it.
Q. A lot of projects coming out of this

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deposition, I see.
Doctor, you would agree that the NDMA once metabolized -- and you've agreed it's reactive -- it's going to attach, if you will, invade the first cell that it can get into that's close by, correct?
A. The metabolite or the parent NDMA?
Q. The metabolite. We're talking about the mutation that results. It's the --
A. The metabolite, other than formaldehyde, methane diazohydroxide is very short lived, so that's going to hit almost where it's formed.
Q. Doctor, you would agree that approximately 95% of our DNA is "junk DNA," isn't it, sir?
MR. SLATER: Objection.
You can answer.
A. I don't know.
Q. Let me ask it this way: You agree that it is approximately only 5% of DNA is coding DNA.
Are you familiar with that term?
A. Yes.
Q. And you agree that only if coding DNA

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is mutated that goes on checked, that's the only DNA that could result in a malignant transformation; agreed?
A. That's the theory, yes.
Q. If the mutated NMDA -- let me strike that.
If the metabolized NMDA [sic] reacts quickly to a cell nearby and it's junk DNA, it's not going to have any ill health effects regardless.
Correct, sir?
MR. SLATER: Objection.
You can answer.
A. I don't know.
Q. Okay.
Because you're not a genotoxic impurities expert, correct?
A. Well, I'm not a microbiologist, if that's what you're asking.
Q. You are not a genetic --
A. I don't know whether an effect on so-called junk DNA is necessarily innocuous.
Q. Yes, sir.
Can we agree you're not a DNA repair expert?

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A. Yes.
MR. SLATER: Objection.
MR. FOWLER: I wasn't quite done with that Gombar article. If we could put up what was 24, I want to look further at 4369. I'll let you know when to take that down. I've got a few questions, please.
THE VIDEOGRAPHER: What do you mean by 2369? Sorry.
MR. FOWLER: 4369 is the page.
THE VIDEOGRAPHER: I'm sorry.
I thought you said 20.
MR. FOWLER: I probably did.
BY MR. FOWLER:
Q. Okay.
You see the first full paragraph begins "We have attempted ..."?
A. Yeah, barely.
Q. Yes, sir. There it goes.
MR. SLATER: Can we blow that up, please?
MR. FOWLER: I think it's blown up.
Q. Doctor, it states "It is well established that NDMA must be metabolized to the ultimate methylating species to exert its toxic

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effect."
Correct?
A. Probably to assert its carcinogen.
Q. And you're --
A. I don't know whether the toxicity of NDMA is necessarily related to the methylating species as opposed to formaldehyde. I don't think that's known.
Q. Doctor, what percentage of the NDMA metabolizes to formaldehyde as opposed to the methylating species?
A. One hundred percent.
Q. So 100% is formaldehyde and 100% is this methylating species?
A. Yes.
Q. Two halves equal three? Doctor, how can two things both be 100%?
A. For each? Okay. Maybe I wasn't too clear, but for each molecule -- let's put it this way: The first thing that happens is that the methyl -- hold on a second, please.
MR. FOWLER: Yes, sir.
(Discussion off the stenographic record)
THE WITNESS: I'm back.

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A. So the first thing that happens is that the P450 catalyzes the hydroxylation of the methyl group to give it alpha hydroxymethyl dimethylnitrosamine. That intermediate has a lifetime of a few seconds and it decomposes spontaneously to formaldehyde and methane diazohydroxide. Methane diazohydroxide is the methylating agent in its DNA and the formaldehyde is formaldehyde.
So for every molecule of NDMA that is metabolized, you get one molecule of formaldehyde and one molecule of methane diazohydroxide, methylating agent.
THE WITNESS: Hold on a second.
MR. FOWLER: Yes, sir.
THE WITNESS: Okay.
Q. Does the formaldehyde form the O6-methylguanine mutation, sir?
A. No. That comes from the methylating agent.
Q. Yes, sir.
In any of the literature that you've relied upon in your report or that you've reviewed and is not part of your report, has any literature about NDMA -- let's talk about the dietary

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studies.
Has any literature ever blamed the formaldehyde as being a carcinogenic factor to -- let me leave it at that -- as being a carcinogenic factor in those studies?
A. No. In general it's not, no. That's true.
Q. Okay.
A. No literature. It doesn't mean that it doesn't play a role. Nobody has thought of it.
Q. Okay.
A. Maybe they thought about it, but if they thought about it, they didn't do anything about it.
Q. Fair enough, sir.
Let's scroll down that page just a little bit further. Right above the formula, the paragraph starts "In spite of ..."
Doctor, you see this statement, "In general, the smaller species" -- and we're talking about the Dr. Gombar's pharmacokinetic studies on things like beagles, hamsters and monkeys even -- it states "In general, the smaller species tended to show lower bioavailability than larger species."

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Any dispute there, sir?
A. No.
Q. And Doctor, you see if it's assumed that NDMA is cleared solely by hepatic metabolism, the bioavailability will depend upon the clearance and the hepatic blood flow.
You agree with that as well, right?
A. Sure.
Q. And is the blood flow in primates -- in particular, the hepatic blood flow in primates -- the same, greater, lesser than humans, sir?
A. I don't know.
Q. Wouldn't it be important to understanding anything you want to extrapolate from these pharmacokinetic studies to understand what the hepatic blood flow is in --
A. Probably. Probably would be.
So what's your point?
Q. That you didn't -- while you're relying on these for the statement that in humans there's high systemic clearance and high oral bioavailability, you didn't make any effort to determine whether that data can be fairly extrapolated from the Gombar studies, did you?

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A. No, I didn't.
Q. If you look -- the last paragraph on this page -- I'm sorry. In that column, sir -- you see wide interspecies -- there you go, that last one in the first column. Perfect.
It states "The wide interspecies difference in bioavailability in NDMA is difficult to explain."
Do you see that, Doctor?
A. Yes.
Q. You would agree that there's interspecies differences with humans compared to any of the animals Dr. Gombar studied with his PK analysis.
Correct, sir?
A. Sure.
Q. Doctor, do you believe that the lung plays any role in the clearance of NDMA?
A. Administered orally?
Q. Yes, sir.
A. It seems unlikely, but it could.
Q. If we could look to the last paragraph in the second column, do you agree with the statement, Doctor, that it is an oversimplification to focus solely on

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pharmacokinetics when you're trying to do a risk assessment, if you will, of NDMA's bioavailability?
A. Sure. It's complicated.
Q. But it says to base risk on dose alone is also an oversimplification.
Do you agree with that, sir?
A. Well, sure, but I mean, you know, dose response is very important in carcinogenesis. You know, this Gombar study was published before the Peto study, if I'm not mistaken.
So, I mean, we do know a lot about the dose response characteristics of NDMA in laboratory animals, particularly rats. Also mice and hamsters. So we know a lot about that, so I mean, you know, this very general statement here was probably made in response to a reviewer, so, you know, just because something is written like in the discussion session of a paper doesn't mean that it's necessarily engraved in stone. So sure, it's an oversimplification to focus solely on pharmacokinetics.
MR. FOWLER: We can take that exhibit down.
Q. Doctor, returning to your statement

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on page eight of your report where you were attempting to opine that NDMA has a high systemic clearance and high oral bioavailability in humans, the only studies that you're pointing to, if we look at sites 21, 22, 23, 24, 25, it's Gombar, Gombar, Gombar, then a Dr. Anderson article.
Is that the -- is there anything else, sir, to support an opinion that there's high systemic clearance and high oral bioavailability of NDMA?
A. There are other articles, yeah. I don't think I got them all here. There's quite a bit of literature on pharmacokinetics and NDMA. You know, I was a little selective here. This is not a comprehensive review. But, you know, systemic clearance by the liver is kind of a common observation.
Q. You would agree, Doctor, that the systemic clearance in oral bioavailability depends on the dose, correct?
A. Yes.
Q. And you can point to no study that evaluates a low dose of NDMA and NDEA and arrives at any conclusion about its bioavailability or systemic clearance.

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Fair statement?
MR. SLATER: Objection.
You can answer.
A. No, that's wrong. You're just talking about all kinds of low-dose studies.
Q. Do those studies speak to bioavailability, sir?
A. Sure they did, yeah.
Q. Bioavailability is --
A. When, you know, you have a low dose given to a rat and it's orally and it's metabolized significantly in the liver, then the bioavailability of the test compound to other tissues is very low.
Q. Any such data would have to be extrapolated to humans based upon the hepatic blood flow, correct, sir?
A. Well, sure.
Q. Any dose given to a mouse or any rodent or other species would have to be adjusted to evaluate a low dose in humans, correct?
MR. SLATER: Objection.
Lack of foundation.
You can answer.
MR. FOWLER: Let me withdraw the question, sir. I think you've answered --
MR. SLATER: Counsel, I'm not looking to argue with you or anything. I just want to establish something so I understand.
I asked the videographer how long we're at at this point and how long Mr. Fowler has been going. I think it's probably 45 minutes approximately.
MR. FOWLER: We don't have to guess. What's the number? How long have we been on the record?
THE VIDEOGRAPHER: If you guys wouldn't mind, I could go off the record so I could give you an exact number.
MR. FOWLER: Apparently, that's important right now, so let's do that.
THE VIDEOGRAPHER: The time is 6:27. We're going off the video record.
(Recess taken)
THE VIDEOGRAPHER: The time is 6:33. This begins media seven.
You may proceed.
Q. Doctor, switching gears again, sir, with regard to the FDA workshop that you participated in, did FDA provide you with any

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written materials in advance or even the questions in advance, sir?
A. Yes, the questions.
Q. Did you share those questions with anyone?
A. No.
Q. What has been marked as Exhibit 12, the FDA's summary on that workshop, sir, did you get -- did you get an advance copy to review and comment upon?
MR. SLATER: Wasn't he questioned on this document already, sir? So now you're going back into the FDA document? Okay.
You can answer the question.
I'm writing to the court.
A. Yes. I'm not sure what you mean by advance copy.
Q. Did you get a draft to review and comment before FDA published it to the --
A. Yes. Yes.
Q. And did you take the opportunity to review it?
A. Yes.
Q. Did you have any comments or changes?
A. Nothing -- nothing substantial. I

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may have had some minor changes, but in general, it was a good summary.
Q. How did you communicate those changes to FDA?
A. Email with the -- I forgot her name right now.
Q. That's fine, sir.
Did you send a red line document or did you type some summary in an email?
A. Summary in an email.
MR. SLATER: Just for the record, I object to this entire line of questioning. This document was thoroughly addressed by Mr. Trischler, so this is clearly duplicative.
The fact that you may be finding a different question that's not identical to Mr. Trischler's doesn't mean that this shouldn't be left alone, as Mr. Trischler covered this subject.
You could continue.
Q. Do you still have that email, Doctor?
A. I don't know.
Q. I will just make a request on the record -- and I'll follow up with counsel -- that

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we'd like a copy of the email with your edits to the draft summary statement.
A. I don't think they were specific, but anyhow, I'd have to go back and look.
Q. Fair enough --
A. It wasn't, like, line 35, change this to that. In general --
Q. Okay. That's helpful. Yes, sir.
A. -- I agreed with her summary. Very comprehensive.
Q. Right, but you indicated you did have changes and you did communicate back to FDA with regard to your response to the draft, correct?
A. I believe so.
Q. I'll make that request offline, sir.
At the time that you reviewed the FDA summary, did you have the transcripts available to you?
A. I didn't review the transcripts.
MR. FOWLER: Now, let's put up Exhibit 12, the FDA summary. Just a couple things I wanted to clarify from your prior testimony.
THE VIDEOGRAPHER: Counsel, I have as Exhibit 12 the "Critical Review of Major

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Sources of Human Exposure." I believe it may be 13. Do you mind if I put 13 up to confirm?
MR. FOWLER: Yes, please.
THE VIDEOGRAPHER: This is Exhibit 13.
MR. FOWLER: Okay. Thank you.
Q. I'll direct your attention to page four, last paragraph.
Doctor, you recall the discussion about endogenous and exogenous sources of NDMA? Do you recall that, sir?
A. Yes.
Q. Do you recall the FDA's statement "To calculate the risk, it's imperative to determine endogenous formation and understand the pharmacokinetics of nitrosamine formation and distribution"?
A. Yes.
Q. We were just speaking to the pharmacokinetic --
MR. SLATER: Counsel, why are you rehashing? This document and this subject was already addressed by Mr. Trischler.
Again, this is duplicative.

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Q. Do you agree that it's important to understand the endogenous formation and the level of endogenous formation? Correct?
A. Yes.
Q. And you -- during the panel, when the question is presented to the group, each of you has an opportunity to respond to the question at hand, correct?
MR. SLATER: Objection.
A. Actually, it was very directed, so I mean certain people -- it was all outlined beforehand who was supposed to respond to which questions and when. It was very scripted. Not scripted, but -- I don't know. I can't think of the word. But basically, you were told when to speak.
Q. Doctor, you would agree that the body sees an NDMA molecule as is and doesn't distinguish its origin, whether it be from food, endogenous or from pharmaceuticals, correct?
MR. SLATER: Objection.
You can answer.
A. Yes.
Q. And the cumulative exposure that contributes to the response is the essential part

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of the valuation.
Would you agree with that?
MR. SLATER: Objection.
A. Yes.
MR. SLATER: Cumulative exposure was discussed earlier as well, counsel.
Q. Doctor, you believe that the -- strike that.
During the testimony, you were given an opportunity to respond on the question of endogenous formation.
Do you recall what you testified you believe the level was?
MR. SLATER: Again, objection.
This has been covered. Mr. Trischler went through that presentation.
You can answer.
I'm continuing to type my email to the court. I regret it that this is necessary.
Q. Doctor, do you recall what you testified to the levels of endogenous formation being?
A. I don't recall the exact thing, but, you know, the literature indicates that there is

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considerable endogenous formation of nitrosamines that are not metabolized. So my -- excuse me.
Q. Yes, sir.
A. My thinking was that we should really learn more about the endogenous formation of nitrosamines such as NDMA that are metabolized and that was the point I was trying to make at the FDA meeting.
MR. FOWLER: Thank you. Let's take down this exhibit. Please put up the day one transcript.
Q. Doctor, when you were testifying at the FDA panel, you understood that your words were being transcribed just as they are today, correct, sir?
A. Yes.
Q. And while you weren't under oath, it was your -- you were certainly doing your best to speak the scientific truth, correct?
A. Yes.
Q. And you said earlier -- several times, I think -- that you had no bias coming into that panel, notwithstanding your retention by Mr. Slater.
Do you recall that?

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A. Correct.
Q. So you answered your questions --
MR. SLATER: Counsel, can we stop for a second? I apologize --
MR. FOWLER: No, we can't stop today. We can't stop right now. I'm in the middle of a question.
MR. SLATER: I object, Counsel. You're not -- this isn't -- I'm really just telling you -- I need to tell you you have on the transcript -- or on the screen the same transcript and you're asking about bias, which he was questioned about already.
So that's the third area where you're now in the same question. Therefore, we're going to stop the deposition. This email is going to go to Judge Vanaskie and I'm asking to terminate the deposition because of this conduct --
MR. FOWLER: I'm reclaiming my time.
Q. Directing your attention to page --
MR. SLATER: We're done.
MR. FOWLER: No, we're not.
MR. SLATER: Go off the record.
I'm stopping the deposition and we're

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going to wait for Judge Vanaskie --
MR. FOWLER: I'm in the middle of a question with this witness.
Q. Page 159, please --
MR. SLATER: No, you're not. You're done.
Dr. Hecht, don't answer the question.
This is harassing and in violation of Judge Vanaskie's order.
I'm going to email him. Hopefully he'll be available and then we'll go from there.
MR. FOWLER: I'm going to make a proffer on the record that I'm attempting to show that the doctor's testimony at this FDA hearing is completely inconsistent with his testimony today.
I'm entitled to show him this transcript and ask him why he testified differently at the FDA.
MR. SLATER: I'm directing him not to answer.
MR. FOWLER: If you want to call the Judge on that, we can.
MR. SLATER: Please stop the record.

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I'm writing to Judge Vanaskie.
MR. FOWLER: I would further proffer I have additional questions based on the doctor's testimony at the FDA hearing, I have questions based upon the doctor's testimony with regard to the Peto study, among others, and moreover, I have questions about Dr. Hecht's testimony with regard to Dr. Johnson's PDE and the threshold.
I have areas to cover that have not been fully explored.
I'm asking you to reconsider letting us finish this deposition --
MR. SLATER: I'm writing to the judge.
MR. FOWLER: I don't -- you can keep telling me that, Adam. I'm asking you to reconsider and let us finish this deposition. I don't think we're wasting anyone's time other than right now.
MR. SLATER: You can't commit to a stop time. You want to be able to go on forever --
MR. FOWLER: How can I commit to a stop time, Adam? I've never heard you commit

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to a stop time --
MR. SLATER: Sorry. You're so angry. Don't be so angry. I'm just trying to --
MR. FOWLER: You've been screaming since I started questioning this witness.
MR. SLATER: You know, I feel bad for the court reporter.
I don't know what to tell you. If you want me to talk, I will. If you want to talk, you can. But I'm trying to type and email on my iPhone.
I think that the ruling has been violated. I think I have good grounds for a protective order. I'm asking for one.
THE VIDEOGRAPHER: Would both sides like me to go off the video record?
MR. SLATER: Do you have my proffer, Madam Court Reporter?
THE COURT REPORTER: I have what you guys have been saying.
MR. FOWLER: Fair enough. Thank you.
MS. KAPKE: This is Kara Kapke. I also have a few follow-up questions, but they should not last more than ten to 15 minutes.
MR. SLATER: Ten to fifteen minutes?

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Okay.
MS. KAPKE: Five to ten probably. Maybe not even that long.
MR. SLATER: I'm just changing my email. Thank you.
THE VIDEOGRAPHER: Counsel, would everyone like me to go off the video?
MS. LOCKARD: Yes. Off the record. And can you give us a count of how long we've been going?
This is Victoria Lockard speaking.
THE VIDEOGRAPHER: The time is 6:45. We're going off the video record.
(Recess taken)
THE VIDEOGRAPHER: The time is now 657.
This begins media eight.
You may proceed.
MR. FOWLER: Can I please get that exhibit back? Day one transcript, FDA panel.
Please turn to page 159.
Q. When we stopped, Doctor, I was asking you if you recalled what you said at the time of the panel about the endogenous production.
Let me direct you to lines 16 to 20.

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You state "So I think with regard to the question of endogenous formation, which is critical here because there are really high levels in endogenous formation, maybe we do not have to be that concerned about the low levels present in drugs."
Have I read your testimony correctly, Dr. Hecht?
A. Yes.
MR. SLATER: Before you answer, Doctor, objection.
I'm asking you to put the full page up there so Dr. Hecht can see the full context, not just this little snippet. Let's give him the whole page, let's let him see the context and --
MR. FOWLER: Absolutely.
Q. So Doctor, the lead-up question for, as you recall, had to do with the endogenous formation of NMDA [sic] and speaking about the biomarkers and the adducts.
The question before you responded was "Can we have more discussion of what you think of all the biomarkers that you have discussed today that could be more appropriate for nitrosamines?"

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As your counsel said, you start your answer "I think DNA adducts would be good to look at. You think we have the technology to reliably quantify DNA adducts with high-res mass spectrometry and we also have the knowledge based on years of study about artifact formation."

Then you state what you said about the endogenous formation.

Does this refresh your recollection of how you characterized the endogenous formation of NDMA at the FDA panel, sir?

A. Yes.

MR. SLATER: Objection.

Before you answer, Doctor, please let me object.

Objection. Okay? Objection. Lack of foundation. It's a very misleading question, but we'll come back to it, Mr. Fowler. You and I both know that.

You can answer, Dr. Hecht.

Q. Doctor, do you recall this discussion at the FDA panel?

A. Yes.

Q. And do you recall the issue of what levels of endogenous formation NDMA there is?

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A. Not NDMA in particular. So what I was referring to in that panel discussion was that there's significant of data for the endogenous formation of nitrosoproline and other nitrosamines that are not metabolized. We could determine this by simply measuring other levels in urine after giving people the precursors and sodium nitrite, as an example.

For dimethylnitrosamine and other dialkyl nitrosamines, which are extensively metabolized, we don't know how much endogenous formation there is and what I was trying to say in the FDA meeting was that what a real need that we have is to develop the technology by which we would be able to accurately determine how much endogenous formation there was of compounds like dimethylnitrosamine.

So, you know, I was speculating. I speculated that the amount that's formed endogenously might be greater than the exogenous amounts, but we don't know and that was my point. We need research. That was my point. Nothing else.

Q. Have you completed --

A. I didn't say that there was -- I

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didn't say that there was higher endogenous formation or that there was lower endogenous formation. I didn't say any of these things.

What I said was that we need to develop the technology, the research to assess endogenous formation. That way, we would be able to know whether the endogenous formation of compounds like dimethylnitrosamine really was.

Right now, we don't know what it is. So that was my -- that was a message I was trying to deliver.

Q. Have you completed your response, Doctor?

A. Yes.

MR. FOWLER: Can I have that sentence that begins with "So ..." blown up, now that we've seen the whole page?

MR. SLATER: I'd like to keep the whole page on the screen, frankly, because now we can't see the full context.

Q. Doctor, can you read if we don't blow that up okay?

A. Yes.

Q. Okay.

You see the sentence "So I think with

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regard to the question of endogenous formation ..." that we were looking at?

A. Yes.

Q. Okay.

You state "which is critical here."

Are you talking about here being the issue with NDMA and valsartan?

MR. SLATER: Objection.

Lack of foundation.

A. No. I was talking about generally. Okay? Not necessarily about valsartan. I was talking about generally for nitrosamines.

Okay?

Q. Okay, sir.

A. We know --

Q. You've answered the question --

MR. SLATER: Stop.

Please continue to answer, Doctor.

A. Let me finish?

Q. Certainly, Doctor.

A. We know from a significant amount of data that there is endogenous formation, nitrosoproline and other nitrosamines that are not metabolized. We can determine this readily. It has been done. There's a lot of solid data out

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there. We don't have this data for the dialkyl nitrosamines that are sensibly metabolized such as dimethylnitrosamine. We don't have the data.

So we don't know whether endogenous formation of dimethylnitrosamine is zero or whether it's the same as the exogenous exposure or more. We don't know.

That was my point. So how it's written, how you interpret what's written, I don't know. But that was my point.

Q. Thank you, Doctor.

Help me understand the last part of that sentence, please. "Maybe we do not have to be that concerned about the low levels that are present in drugs."

Did I read that correctly?

A. Yes.

Q. And we're talking about the NDMA levels in the valsartan that you're there at the panel for, correct?

A. That's right.

MR. SLATER: Lack of foundation.

Q. Thank you. Did we get that answer --

A. As I tried to explain, sir, we don't know. Okay? What I was trying to say in that

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panel discussion was that we need to develop the technology and do the experiments so we can find out the extent of formation of -- of endogenous formation -- of dimethylnitrosamine and other dialkyl nitrosamines that are rapidly metabolized. That's what I was trying to say.

Q. Yes, I've gotten that, Doctor. I'm focused now on how you concluded the sentence, that "Maybe we don't have to be concerned about the low levels present in the drugs."

Can you explain that, please?

A. You're not listening because I have explained it. Okay? Listen to what I'm saying. Okay?

If the amount of endogenous formation of dimethylnitrosamine turn out to be very high, then we wouldn't have to be concerned. But we don't know.

Q. Thank you, Doctor.

A. We don't know. We have zero data.

Q. Well, respectfully, you disagree with the data that your colleague presented at the FDA panel as to the level of 400 micrograms in the -- produced endogenously.

You just disagreed with that.

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A. Four hundred micrograms of what and which colleague?

Q. Doctor -- well, I'll not pronounce his name right. It starts with a K. Doctor -- can you help me, sir?

A. Kokkinakis.

Q. Yes, sir.

Do you recall the slides that he put up at the FDA panel on endogenous formation?

A. Yes, I don't agree with those at all. I think they're flawed.

Q. Right.

To your point, Doctor, if the level is high -- and would you agree a level greater than 100 micrograms a day would be considered high in the context that you and I are speaking of now?

A. Yes.

Q. The point is if it's that high and we add 10, 15, 20 micrograms to that endogenous supply of NDMA, you would not consider that to be an increased risk of cancer compared to the endogenous source, correct?

MR. SLATER: Objection.

A. I don't know what you're talking about, risk of cancer. I don't know. I mean, the

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point is -- the point that I'm making -- and this is what I believe. Okay?

In this deposition, we don't have reliable data on endogenous formation of dimethylnitrosamine and until we have that data, we cannot say that the exogenous formation such as through valsartan is unimportant. We can't say that because we don't have the data. The data that Kokkinakis quoted, I do not believe it's correct.

Q. Doctor, do you agree that the panel and FDA was concerned that it would make no sense to the public, including the scientific informed public like yourself, that if FDA set a limit of NDMA at, like, 96 nanograms and the body is producing 400 micrograms a day, that it could erode the confidence in FDA's risk assessments because that would make no sense to the public? Do you recall that discussion?

MR. SLATER: Objection.

A. Well, sure it would, but we don't have the data.

Q. Right.

A. If we had -- if we had reliable accepted data on, you know, that NDMA was formed

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to the extent of 400 micrograms per day in humans, then FDA would not have put out the thing about 96 nanograms.
Q. Did FDA impanel this workshop so that they might understand and get scientific input from leaders in the different areas about what these levels are? Isn't that why it was one of the questions posed?
A. Yes.
MR. FOWLER: Let me have day two transcript, please.
Q. Directing your attention to page 15, we're going to look at line nine through 18. It states here, Doctor -- I hope you can see it because I don't want to blow it up, I want to leave the whole page there.
It states that the balance of evidence seems to be that the amount consumed by the drugs -- consumed in drugs is minuscule or at least very much smaller than one expects from intake in water and especially in foods and I think it would send a confusing message to consumers, citizens in general, to tell them that the body somehow knows whether a given molecule, any given nitrosamine comes from a drug taken by

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necessity or food voluntarily.
Do you see that, Doctor?
A. Yes.
MR. SLATER: Objection.
Lack of foundation.
Inaccurately read.
Q. You don't disagree with that, Doctor, right? That's what you and I have been speaking about?
MR. SLATER: Objection.
A. We need the data. You know, we need the data. Intake from water is very unclear and endogenous formation is very unclear.
The only place where we really have reliable data, you know, other than valsartan and the other drugs obviously is food.
Q. Yes, sir.
But my question was actually do you agree that the issue here was that it could send a confusing message if FDA is setting an acceptable intake limit that is far below what our body creates naturally?
That's my question, sir.
A. Sure, but we don't have the data and they know that. They know that --

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MR. SLATER: Counsel, stop.
A. That's why they made the 96 nanograms.
MR. SLATER: Counsel, we're going to stop the deposition.
A. I mean, really, honestly, we have been -- we have been through this before.
MR. FOWLER: I honestly couldn't hear either one of you.
THE WITNESS: I'm starting to agree with Adam.
MR. FOWLER: I couldn't hear Adam or you, sir.
MR. SLATER: Judge Vanaskie has just asked to call -- Mr. Fowler, we're breaking -- let's go off the record.
Judge Vanaskie has asked us to include him in a phone conference and he gave the number. We need to call him. I don't have a call in number that I can give to anyone, so I don't know what to do. We got to get him on the phone. He wants to speak right now.
THE VIDEOGRAPHER: Would you like to go off the video first?

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MR. SLATER: That's fine.
THE VIDEOGRAPHER: The time is 7:12. We're going off the video record.
(Recess taken)
THE VIDEOGRAPHER: The time is now 727.
This begins media nine.
You may proceed.
Q. Dr. Hecht, do you have an opinion whether or not NDMA is a threshold compound?
Do you understand the question?
A. Threshold compound? You mean whether there's a threshold for carcinogenicity?
Q. Yes, sir.
MR. SLATER: Objection.
Asked and answered.
You can answer.
A. I don't know of any evidence that there is.
Q. Do you have an opinion one way or the other, sir?
A. I believe there is no threshold based on the studies of Peto, Grasso and others.
MR. FOWLER: Well, let's mark --
A. The large rat dose response study.

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They concluded that there was no indication of a threshold.
MR. FOWLER: Let's mark Peto 1991 B.
Q. Doctor, while that's being called up here, I think we're -- as far as our nomenclature goes, I think we're in agreement that a threshold level is one below which there's no evidence of carcinogenicity. Just so we're on the same page, sir.
A. Yes.
THE VIDEOGRAPHER: Counsel, just wanted to check. The document, I just want to check.
The document you're looking for, does it have at the top of the page "Cancer Research"?
MR. FOWLER: It does. It's called "Dose and Time Relationships for Tumor Induction in the Liver and Esophagus," etc.
THE VIDEOGRAPHER: Let me know if this is the right one here.
MR. FOWLER: No.
THE VIDEOGRAPHER: Okay.
MR. FOWLER: It's 1991 A.
Q. Doctor, while this is coming up, do

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you agree that the concept, if you will, of permissible daily exposure of PDE, the PDE itself is a level below which -- let me start that again.
The PDE would be considered a threshold level in that nomenclature, sir?
MR. SLATER: Objection.
This topic was asked and answered and covered earlier.
You can answer.
A. Repeat the question.
Q. Is a PDE another term for a threshold level?
A. Essentially, yes.
Q. I understand you did not read Dr. Johnson's article, so is it fair to say that you don't know whether that article establishes any sort of threshold, sir?
A. Which article was that?
Q. Dr. Johnson's 2021 --
A. I hadn't read that, no.
Q. Yes, sir.
So you're not here to say whether or not that data demonstrates a threshold at low doses?
A. I'm not, no.

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Q. And would you defer to a genetic toxicologist to interpret such data when calculating a PDE?
MR. SLATER: Objection.
You can answer.
A. A genetic toxicologist?
Q. Yes, sir.
A. Would I defer to a genetic toxicologist? I'm not sure.
Q. You've never done a benchmark dose evaluation, have you, sir?
A. I think I mentioned this repeatedly today.
MR. FOWLER: Just waiting on Peto, sir. I'm just trying not to --
THE VIDEOGRAPHER: Counsel, I only have one document, the one that I pulled up, that was labeled with P-E-T-O for Peto.
MR. FOWLER: Okay, sir. I'll forge ahead without it.
Q. Doctor, do you recall that in the Peto study, there was a level of -- let me start that again.
The Peto study was a large cancer bioassay, correct?

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A. Yes.
Q. It administered a variety of doses, some of which until that animal died, correct?
A. Yes.
Q. And it had a control group, yes?
A. Yes.
Q. And at low doses, if the number of subject animals produced fewer tumors than the background rate of the control group, would you say that there's evidence of a -- that that supports evidence of a threshold?
Do you understand my question, sir?
A. No.
Q. It was a bad question. I'll try again.
If the dose levels from let's say 0.001 through 0.087, as reflected in table seven of Peto, produced tumors fewer than the control group expressed, do you agree that you cannot attribute the tumors produced at those low doses to anything other than background?
MR. SLATER: Objection.
I object for multiple reasons, including you're quoting a table that nobody can see and I object to the multiple parts of

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the question.
You can answer if you can.
A. I really can't answer that without looking at the data. But I do recall very specifically that Peto said either in the abstract or in the discussion that there was no evidence of a threshold, quote, unquote.
Peto is a statistician who was very well respected, so I take his word.
Q. Yes, sir.
Doctor, if in an animal study the doses produce fewer tumors than the control group, can you conclude anything about the causation of those low doses, sir?
A. I would have to look at the data. I don't know what data you're talking about.
Q. Is there any conceivable study that you can imagine where the dose group revealed fewer tumors than the control group and a causation determination can be made? Can you envision anything like that, sir?
MR. SLATER: Objection.
Multiple reasons.
You can answer.
A. I don't know.

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Q. Why are control groups used in animal studies, sir?
A. Because it gives you a reference point to compare to your treated group.
Q. And why is that important?
A. Because, you know, there might be some tumors that form in the untreated animals for reasons other than the material that you're administering due to other factors, endogenous factors and whatever.
So you have to have a control group because, you know, tumors will develop in various organs of animals with old age, laboratory animals with old age, so you need the control group as a comparison.
Q. Thank you, sir.
Let me direct your attention -- shifting gears back to your report, please -- I'm going to direct your attention to page 11.
Let me know when you're there, sir.
A. I'm there.
Q. The middle paragraph -- and this is Exhibit 1 -- in the middle paragraph, at the bottom, you state "Given sufficient exposure to NDMA and NDEA, as with the levels found in the

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contaminated valsartan (see below) the formation of these DNA adducts would be sufficient to cause mutations in cancer in exposed humans."
Have I read that correctly, sir?
A. Yes.
Q. You would agree, sir, that the number of adducts is dispositive for a cell to undergo a malignant transformation; isn't that correct?
A. Is dispositive? What was your -- I didn't hear --
Q. I'll rephrase, sir.
A. The number of adducts is what?
Q. There is a minimum number of adducts that must be -- that exist in a cell before it undergoes a malignant transformation, correct?
A. A minimum number? Sure. I mean, there is a number. We don't necessarily know what it is.
Q. Yes, sir. And one O6-methylguanine mutation can be the result of one metabolized NDMA molecule, right?
A. Correct.
Q. Do you have any reason to dispute that there are roughly 600 adducts of O6-methylguanine at any given time in a cell

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absent exogenous NDMA?
A. Where did you get that from?
Q. My question is do you have any reason to dispute that, sir?
A. Yes.
Q. What is your basis?
A. I don't know where you got that number from. Just made it up or what? Where did you get the number 600 from?
Q. You agree there's a baseline number of O6-methylguanine adducts in a cell at any given time, sir, right?
A. Baseline number? What is that?
THE WITNESS: Hold on, sir.
(Discussion off the stenographic record)
Q. I'll move on, Doctor.
A. Sorry.
Q. Referring to page 11, I'm just interested in what the number of DNA adducts you are referring to in that sentence.
You don't give any level, sir, and that's what I'm asking --
A. Which sentence now?
Q. The one we read in page 11 of your

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report, "Given sufficient exposure to NDMA and NDEA, as with the levels found in the valsartan, the formation of these DNA adducts would be sufficient to cause mutations."
My question is how many adducts, sir?
A. I don't know. One. One adduct in theory.
Q. I'm sorry. You broke up.
One more time?
A. One adduct in theory is enough.
Q. You would agree that one adduct is subject to DNA repair, correct?
A. Yes.
Q. And if repaired, no risk of carcinogenicity, correct?
A. Not from that particular pathway, correct.
Q. Do you disagree that DNA repair can and does create a threshold level when exposed to low doses of NDMA?
MR. SLATER: Objection.
You can answer.
A. It's a very general question. I mean, there's no doubt that DNA repair is important. You know, when you say does it affect

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the low doses, you know, what's a low dose, what are the conditions. There are many factors, but we know that DNA repair is important.
You know, there's a lot of hand waving in your statement.
Q. Thank you, sir.
I've now found where the 600 came from -- I apologize -- earlier.
Were you familiar with an article by Dr. Krause and McKeene, et al, from 2019 entitled "Immunological and Mass Spectrometry Approaches to Determine Thresholds of Mutagenic DNA Adduct O6-methylguanine and VBo"?
Are you familiar with that article, sir?
A. Doesn't strike a bell offhand.
Q. Okay.
Thank you, sir.
Doctor, do you agree that potency, the existence of a threshold and dose response are toxicology issues, sir?
A. Yes.
Q. And because you are not a toxicologist, you're not qualified to render opinions on potency existence of a threshold or

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dose response; isn't that correct, sir?
MR. SLATER: Objection.
You can answer.
A. That depends what you mean by qualifications. I'm not a toxicologist. That's true. I don't know that that necessarily excludes me from having opinions.
Q. Yes, sir.
Would you defer to a toxicologist as to the existence of a threshold for NDMA and NDEA?
MR. SLATER: Objection.
You can answer.
A. That would depend who the toxicologist was.
Q. Fair point, sir. Thank you.
Doctor, do you agree that or disagree that the DNA adducts that we're speaking about, this O6-methylguanine, those adduct measurements do not define the location of the adduct in the genome.
Is that a true statement?
A. Yes.
Q. Given that cells have evolved efficient measures to keep gene coding sequences damage free, it's not possible to currently say if

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DNA adducts accrue in a linear fashion in the coding sequences.
Do you agree with that?
A. Yeah, yes.
Q. And for the jury -- I'm sorry.
A. Yeah.
Q. For the jury's purpose, by saying it does not accrue in a linear fashion, that means if you're adding two more NDMA molecules that it will not -- let me start that again.
If you double the NDMA molecules, it doesn't result in a linear uptick of the mutations, correct, sir?
MR. SLATER: Objection.
You can answer.
A. You know, that's a complicated question because we know that the dose response for NDMA -- and NNK, for that matter -- in mice is a hockey stick --
Q. Yes, sir.
A. -- kind of picture because when the O6-methylguanine DNA methyl transfer is succeeded -- in the activity that is succeeded -- then the cancerous mutations will increase more rapidly, so it's not linear. It's more like this.

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Q. And a hockey stick, I've got a couple behind me, they're long and flat and then the blade goes up at the end, correct, sir? It's a line with an uptick at the end where the hockey blade would be? That's how it gets its name?
A. Yes. You have a slowly increasing amount which would be similar to the blade and then when you reach a certain point, the increase is greater, so that's where the hockey stick comes from.
Q. Yes, sir. Thank you.
Shifting gears a little bit, Doctor, just to keep moving, do you agree that if more than one nitrosamine are present -- let's do it this way.
If NDEA and NDMA are both present in the body at the same time, do you agree that their actions, if you will, will be additive and not synergistic?
Do you understand the question, sir?
A. Yes, probably. But to tell the truth, I don't think we have good data on that.
MR. FOWLER: Can I have the FDA transcript, day one please?
(Whereupon, Exhibit 25 was marked for

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identification.)
(Whereupon, Exhibit 26 was marked for identification.)
Q. Do you recall this issue coming up in the FDA panel, sir?
A. Not right now, I don't, but sure, I probably do.
Q. I'll try to refresh your recollection. Look at day one and I'll direct your attention, please, to page 143 and in particular, directing you to line 15 through 19.
Do you see your name there?
A. Yes.
Q. I could have it blown up so you could take your time to look at it.
So you say "I agree. Considering the low levels that we are going to be observing, additivity is definitely the default assumption of the molar amounts that are present, so I agree with everything that has been said about additivity."
Do you see that, sir?
A. Yes.
Q. And are you familiar -- I'm sorry?
A. That's what I said.

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Q. You're not -- you have no -- you're not disagreeing with yourself here today, are you, sir?
A. No.
MR. FOWLER: Doctor, let me again switch gears. You could take that down, please.
Q. With regard to your research on tobacco and cigarette smoking, the -- you would agree that there are -- there have been identified specific cancers which are attributed to cigarette smoking, correct, sir?
A. Yes.
Q. And I think you testified earlier there's some 70 carcinogens in tobacco, which include certain nitrosamines, yes?
MR. SLATER: Objection.
A. In tobacco smoke.
MR. SLATER: Objection.
We're now duplicating questioning exactly. I don't appreciate it.
MR. FOWLER: It's just a foundation, Counsel. Trying to orient the doctor as I jump around here.
Q. So Doctor, the carcinogens from

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cigarette smoke, you would agree, are quickly -- quickly enter the bloodstream upon exposure.
Do you agree with that?
A. Yes.
Q. And as a result of --
A. For the most part.
Q. Fair enough.
As a result, they travel throughout the body's tissues, the arterial system, back, venous system.
It's everywhere, correct, sir?
A. It's a very general statement. You know, each carcinogen behaves differently. For example, some may be retained in the lung particles. There may be other factors that affect the absorption into the bloodstream.
Q. Based upon your research, Doctor, you agree that NDMA, as one of those nitrosamines, likewise enters the blood and is transported to various tissue systems in the blood, correct?
A. Yes.
Q. And throughout your research of cigarette smoke and tobacco, none of your studies or any studies that you have seen has identified cigarette smoke-induced tumors as being caused by

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NDMA.
Isn't that true?
A. Correct.
Q. In fact, it's been your publication that the nitrosamines NNN, NNK and there may be a couple more, are the responsible nitrosamines for the cancers that cigarette smoking causes.
Is that a fair statement?
A. No. I've never excluded other nitrosamines.
Q. Okay.
A. I presented data that supports the concept that NNN and NNK cause DNA damage and cancer in smokers and also smokeless tobacco users, but I've never excluded other nitrosamines whatsoever.
Q. Thank you for that clarification, sir.
Can you explain why it is if NDMA is transported through the blood from the cigarette smoke why there's not any evidence that NDMA causes cancer in these various tissues that it reaches through the cigarette smoke as a result of the cigarette smoke, sir?
MR. SLATER: Objection.

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You can answer.
A. We don't know the answer to that.
Q. You agree that the nitrosamines in tobacco smoke or smokeless tobacco have different carcinogenic presentations when administered differently, correct?
A. Yes and no. It's not really correct. It depends -- you can't generalize. Okay? I know too much about this. Some of them -- NNK for example, will affect the lung almost independent of the root of administration, seemingly given by insulation into the bladder and affects mainly the lung. NNN, on the other hand, will affect the oral cavity and esophagus when given in drinking water.
Q. I'm sorry.
A. It's hard to generalize.
Q. For each cancer that you would agree is caused by cigarette smoke, do you agree that that determination was based upon actual data and testing and an evaluation of human tissue and tumors to make that causation connection?
A. Epidemiology, yes.
Q. Well, I'm speaking of actual lab science, Doctor.

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A. Well, you were talking about causation.
Q. Yes, sir.
A. So, you know, the first thing in causation is usually epidemiology.
Q. For cancers that are known to be caused by cigarette smoke, sir, have the determinations as to the specific types of cancer, to your knowledge, been evaluated in a -- by pathologists in the laboratory to reach any conclusions at all, sir?
A. Repeat your question.
Q. Well, outside of epidemiology evidence, I'm trying to understand whether the causal link between cigarette smoke and these cancers that you've identified has been identified through toxicology studies of human tissue in in vivo, in vitro, but using human tissue to make that determination?
A. Yes, absolutely.
Q. Okay. And -- I'll just leave it at that.
No, I won't.
There's no such similar study with regard to any determination of NDMA and any

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cancers that it could allegedly cause in humans, correct?
A. Oh, there are multiple studies of NDMA metabolism by human tissues, organ culture studies. Also, sub cellular fractions. Yes, multiple studies published many years ago.
Q. Notwithstanding the agreement today, Doctor, you said several times that the level of NDMA in the pharmaceuticals should be zero?
A. Yes.
Q. Doctor, you don't hold yourself out as any sort of regulatory expert, do you, sir?
A. No.
Q. Do you know what a drug master file is?
A. Not exactly.
Q. Do you know what criteria FDA uses whether or not to approve a drug?
A. That's not my area.
Q. So you have no basis for saying whether or not these drugs have been approved or not or if that number should be zero, do you?
MR. SLATER: Objection.
A. I have a basis for saying it should be zero. I absolutely have a -- I absolutely have

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a basis for saying it should be zero because I've looked at the method of synthesis and I've looked at all the data from CHP and the others and absolutely this never should have happened. We shouldn't be here. It should have been zero.

MR. FOWLER: Thank you, Doctor.

I don't have further questions. I'll pass the witness to the next questioner. Thank you so much for your time and patience.

MR. SLATER: You know, if you told me you had a hockey stick, we would have been more easy going. I don't want to get hit by a hockey stick.

MS. KAPKE: Good evening, Dr. Hecht. I'll be very brief. I have a couple of questions.

EXAMINATION BY
MS. KAPKE:

Q. You agreed in response to Mr. Trischler's questions earlier today that valsartan is typically a long-term drug taken chronically.

Do you remember that?

A. Yes.

MR. SLATER: Objection.

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Duplicative.

Q. Understanding that valsartan is typically taken chronically, do you have an opinion about whether acute usage of valsartan containing an NDMA or NDEA impurity could cause a person to develop cancer?

MR. SLATER: Objection.

You can answer.

A. Well, it would be more likely from continuous use because, you know, the cumulative dose would be greater.

Q. Did you evaluate the animal studies with an eye towards duration of use to make an assessment of how long a person would need to take valsartan containing NDMA or NDEA before that NDMA or NDEA exposure could have caused the person to develop cancer?

A. Which animal studies?

Q. Any of them.

A. No, I didn't attempt to make that evaluation. There are many -- there are many animal studies of NDMA. I guess the one that's most compelling is the Peto study. So we know that very low doses of NDMA given over a long period of time to rats can cause a significant

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incidence of tumors.

Q. Let's just use that study. I'll just follow up on that.

How long of a duration of exposure did the rats have in the Peto study?

A. Over two years, I believe it was.

Q. Are there any studies that you are relying on that are acute animal studies?

A. There are single dose studies of NDMA. Sure.

Q. And are -- could you give me -- are they cited in your report?

A. No. My report doesn't go into detail and all of the literature on NDMA, which is very extensive, the carcinogenicity literature --

Q. Okay. Let me just back up --

A. -- they're out there. I mean, there's a huge number of studies on NDMA carcinogenicity and laboratory animals.

Q. Okay.

Let me just back up and ask it this way: You've agreed here multiple times that dose and duration are important.

Is there a minimum number of days a person would need to take valsartan that contain

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NDMA or NDEA in any amount that's relevant to this case before that exposure would cause a person to develop cancer?

A. We don't know. In theory, one exposure is sufficient. We don't know a minimum number of days. We don't know that.

Q. Are there any studies that you are relying on specifically to allow you to extrapolate to duration of use for only a single day as being appropriate to cause cancer in a human?

A. No. I don't believe there is any study like that in a human.

Q. Are there any --

A. There are single dose studies in animals --

Q. And --

A. -- of NDMA.

Q. Are any of those studies sufficient for you to extrapolate to a person who took one pill of valsartan containing NDMA or NDEA and NDMA or NDEA impurity? Can you cite me any such study that is appropriate to extrapolate?

A. No, there's not.

Q. What about the same question for a

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single prescription fill for 30 days?
A. I don't have that kind of data. That would be -- that would be speculation.
Q. And --
A. It's all dose response, so obviously the more frequently the pill contaminated with dimethylnitrosamine was taken, the higher the risk.
Q. Would it be fair to say that a person needed to take valsartan containing an NDMA or NDEA impurity for at least a year before that NDMA or NDEA exposure could have caused that person to develop cancer? Would that be a fair statement?
A. I don't think we know the timeframe. I mean, the study that we talked about before from Germany covered three years, I believe, and they saw an increased risk of liver cancer, but I don't think we know the timeframe. I mean, in theory, everything lines up wrong. You know, one dose should be enough in theory.
Q. Well, in --
A. If everything is wrong, I mean, you know, if your DNA repair is not working right, if you happen to hit the right part of the DNA in the right gene, the right mutation, in theory, it only

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takes one.
Q. Well, what I want to get at is what is your opinion to a reasonable degree of medical and scientific certainty as to the duration of exposure that can cause a person to develop cancer following an exposure to valsartan containing an NDMA or NDEA impurity.
I'm trying to see if you can put a duration limit on that for me to a reasonable degree of medical and scientific certainty.
A. It's very hard to do but, you know, if you force me to give a timeframe, I guess as a minimum I would be, you know, comfortable with one year, but it's very -- very difficult question to answer.
MS. KAPKE: Okay. I have no further questions. Thank you.
MR. SLATER: Let's go off the record.
THE VIDEOGRAPHER: The time is 8:05. We're going off the video record.
(Time noted: 8:05 p.m.)
(Deposition concluded for the evening.)

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A C K N O W L E D G M E N T

I, STEPHEN HECHT, Ph.D., hereby certify that I have read the transcript of my testimony taken under oath in my examination of August 17, 2021; that the transcript is a true, complete and correct record of what was asked, answered and said during this deposition, and that the answers on the record as given by me are true and correct.

_____
STEPHEN HECHT, Ph.D.

Signed and subscribed to before me, this day of 2021.

_____
Notary Public

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CERTIFICATION

I, SARA K. KILLIAN, RPR, CCR, do hereby certify that STEPHEN HECHT, Ph.D. the witness whose examination under oath is hereinbefore set forth, was duly sworn, and that such deposition is a true record of the testimony given by such witness.

I FURTHER CERTIFY that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 23rd day of August, 2021.

SARA K. KILLIAN, RPR, CCR

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
MDL No. 2875
----------x

IN RE:

VALSARTAN PRODUCTS
LIABILITY LITIGATION

----------x

August 18, 2021
9:08 a.m.

Continued Videotaped Deposition of STEPHEN HECHT, Ph.D., taken by Defendants, pursuant to Notice, held via Zoom videoconference, before Todd DeSimone, a Registered Professional Reporter and Notary Public of the States of New York and New Jersey.

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WILLIAM MILLER, Videographer

S. HECHT

THE VIDEOGRAPHER: Good morning. We are going on the record at 9:08 a.m. on August 18th, 2021.

This begins day two of the deposition of Stephen Hecht Ph.D. in the matter of the Valsartan/Losartan Litigation. My name is William Miller from the firm Veritext Legal Solutions and I am the videographer. The court reporter today is Todd DeSimone from the firm Veritext Legal Solutions. All counsel is noted on the stenographic record.

Would the court reporter swear in the witness or remind him that he is still under oath.

* * *

S T E P H E N H E C H T, Ph.D., having been previously duly sworn, testified further as follows:

MR. SLATER: Steve, I think you wanted to put something on the record before we started?

MR. FOWLER: Yes, thanks, Counsel.

S. HECHT

When we concluded yesterday before passing the witness to plaintiff, I just want to confirm on the record that the run time in total at that point on the record was eight hours and 41 minutes as was provided to us yesterday. Is that your recollection as well, Counsel?

MR. SLATER: That is my grudging recollection.

MR. FOWLER: Yes, sir, okay.

MR. SLATER: You see the smile on my face, I'm saying grudging, because we talked about before that I don't know where all the time went.

MR. FOWLER: Perfect. Thank you.

EXAMINATION BY MR. SLATER:

Q. Okay. Is it okay if I begin now? Ready to go, Doctor?

A. Yes.

MR. SLATER: Chris, can you put up the FDA document that had those four bullet points that was used yesterday, please, multiple bullet points I should

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say. Okay, let me start.

Q. Here is a document that you were shown yesterday, Dr. Hecht, regarding, it is actually the FDA's statement about nitrosamine impurities, and what I would like to do is focus where the defense attorney focused yesterday, on the fourth bullet point, if we could, please. Let me get this out of the way.

Do you see that, the fourth bullet point down?

A. Yes.

Q. Okay. For the record, it says "Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains nitrosamines at or below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer."

Do you see what I just read?

A. Yes.

Q. First of all, I want to focus

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on the second half where the FDA says that a person taking these drugs at or below the acceptable daily intake limits is not expected to have an increased risk of cancer.

Am I correct that when the FDA says not expected, they are not saying they will not have an increased risk of cancer?

MR. FOWLER: Objection, form.

A. Yes, that's what it seems to say.

Q. And if I understand correctly, the FDA said that there may be an increased risk of cancer for people who take the pills with contamination above the acceptable levels for what they term long periods of time, correct?

MR. FOWLER: Objection, form, speculation.

Q. That's what the document says, right?

A. That's what it says, yeah.

Q. Am I correct that above the acceptable levels would encompass virtually

S. HECHT

all of the contaminated valsartan at issue and as described in your report where you went through the levels disclosed by the manufacturers in our depositions?

MR. FOWLER: Objection, form, facts not in evidence.

A. I mean, as I understand it, they said the acceptable limit was 96 nanograms per day.

Q. For the NDMA, correct?

A. Right.

Q. And 26.5 nanograms for the NDEA, correct?

A. Right.

Q. And all or virtually all -- rephrase.

Virtually all of the pills -- rephrase.

The manufacturers disclosed their levels and we have them in your report, those levels in virtually all cases exceed those levels, correct?

A. Yes.

Q. So based on this FDA statement,

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those valsartan pills sold by these manufacturers that were above the acceptable levels are deemed by the FDA to potentially increase the risk of cancer, that's what this statement says, right?

MR. FOWLER: Objection to form, mischaracterizing.

A. Yes.

Q. And I will give an example. Why don't we go, just so we have some context, Doctor, do you have your report handy, please? If you have your report, can you turn to page 22. Actually, it starts at the bottom of page 21, for context, where there is a heading ZHP, NDMA and NDEA Levels.

A. Yeah.

Q. And if I understand correctly, these levels are referenced as coming from documents and testimony provided to you by my law firm based on what we learned in discovery in this case, correct?

A. Right.

Q. And let's just look at some of

S. HECHT

the levels. If you look at page 22, in the first full paragraph, about four lines down, there was a chart of testing results of 783 batches from ZHP manufactured between 2011 and 2018 with NDMA levels as high as 188.1 parts per million.

A. Right.

MR. FOWLER: Objection, form, leading.

Q. Let me know if I have -- rephrase.

And my calculation is that 188.1 parts per million in a 320 milligram pill, you would multiply the parts per million by the 320 and we would come up with 60,192 nanograms. Does my math sound correct?

A. Yes.

MR. FOWLER: Objection to form, leading.

Q. And even if we were to look at levels in the next paragraph where it says in the middle of the paragraph "There are a small number of batches with results in the

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single digits with the lowest at 3.4 parts per million per a separate spreadsheet," let's look at 3.4 parts per million, in a 320 milligram pill, my calculation is that would be 1,088 nanograms. Does my math sound correct?

A. Yes.

MR. FOWLER: Objection, form.

Q. Those levels I just gave as examples would far exceed the levels the FDA found to be acceptable, correct?

MR. FOWLER: Objection, leading.

A. 96 nanograms, right.

Q. And let's look at page 25, which is the carry-over from page 24, regarding Mylan, talking about NDEA with levels between 0.1 parts per million to 1.57 parts per million. And my calculation is that at 0.1 parts per million in a 320 milligram pill, you multiply the 320 by the 0.1, you come up to 32 nanograms. Does that math sound correct?

A. Yes.

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MR. FOWLER: Objection to form. You are talking about API, Counsel. Mischaracterizing.

Q. Does that math sound correct?

MR. FOWLER: Same.

A. Yes.

Q. And looking at the upper bound of that range, 1.57 parts per million, for a 320 milligram pill, that would be 502.4 nanograms. Does that math sound correct?

MR. FOWLER: Same objection. You are talking about API numbers. Form.

Q. Does that math sound correct?

A. Yes.

Q. And just to be fair to Mylan's counsel, who was here yesterday, he gave you what he calculated as a mean of 0.47 parts per million, and just assuming that for a moment, for a 320 milligram pill, that would come to 150.4 nanograms. Does that math sound correct?

MR. FOWLER: Objection to form, incomplete, mischaracterizes.

A. Yes.

S. HECHT

Q. Those NDEA levels for Mylan, do they all exceed the limits the FDA set?

MR. FOWLER: Same objection.

A. Yes.

Q. You can put that document aside for a moment, or for now.

Let's go now to the Control of Nitrosamines -- of Nitrosamine Impurities in Human Drugs, Guidance For Industry. We are now at Appendix B, at the end of that document.

MR. SLATER: And do we have this marked as an exhibit previously in the deposition? I can't recall.

MR. GEDDIS: No.

MR. SLATER: Let's mark it as whatever the next exhibit is, please.

THE VIDEOGRAPHER: The next exhibit number is 27.

MR. SLATER: Thank you.

(Hecht Exhibit 27 marked for identification.)

Q. Looking now at the last page of Exhibit 27, I just want to look at the top

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part where the FDA provides their information as to how they calculated the acceptable intake limits. Do you see that?

A. Yeah.

Q. And I just want to focus on the beginning where it says that "The FDA followed the procedures recommended in the ICH Guidance For Industry," and it gives the title of that document, and then says "a compound-specific acceptable intake can be calculated based on rodent carcinogenicity potency data such as TD50 values."

Do you see that?

A. Yeah.

Q. And ultimately that is what was applied based on rat data, correct?

A. Yes.

Q. So the FDA chose to use animal study data to establish the acceptable intake limits for human beings, correct?

A. Yes.

MR. FOWLER: Objection, form.

MR. SLATER: I think now might

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be a good time, let's take that down, and if you could, Chris, let's put up the Johnson study that Dr. Hecht was asked about. I would like to spend a couple of minutes on that, two minutes or so. You can blow up the abstract or at least let us be able to see the abstract. Perfect.

Q. First, Doctor, what I would like to do is read the first sentence or two of the abstract and then ask you a question. It says "A genotoxic carcinogen" -- and I'm going to stop there. What is a genotoxic carcinogen? What does that mean?

A. That is a carcinogen that damages DNA, forms adducts with DNA or otherwise damages DNA.

MR. FOWLER: Objection, form.

Q. "A genotoxic carcinogen, N-nitrosodimethylamine (NDMA), was detected as synthesis impurity in some valsartan drugs in 2018, and other nitrosamines, such as N-nitrosodiethylamine (NDEA), were later detected in other sartan products.

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N-nitrosamines are promutagens that can react with DNA following metabolism to produce DNA adducts, such as O6-alkylguanine. The adducts can result in DNA replication miscoding errors leading to GC greater than AT mutations and increased risk of genomic instability and carcinogenesis."

What I would like to ask you, Doctor, without getting too deep into it, but as much as you would like to explain, what is this telling us, what I just read, about being promutagens and these mechanisms being described, what is that and what is the significance of it?

MR. FOWLER: Objection to form, multiple reasons. Go ahead.

A. Well, it is telling you that all of the data that is out there is very consistent about this particular process, that upon metabolism NDMA and NDEA form reactive intermediates that react with DNA, causing alkylation at the various nucleophilic sites in DNA, one of which is

S. HECHT

the O6 position of guanine.

So it is well established that in animal systems, in all animal systems, if you treat the animal with NDMA or NDEA there will be O6-alkylguanine in the DNA, and that particular DNA adduct is known to cause miscoding, which means that normally where you had a GC, a base pair in the DNA, that will be converted to AT.

This will change the sequence in your DNA and if that sequence change occurs in a so-called oncogene enough to activate the oncogene, such as rats, and cause it to enter into a molecular pathway, that results in uncontrolled growth and cancer.

Q. What you just described, is that controversial in any way in the scientific community?

A. No.

MR. FOWLER: Objection, form.

A. Absolutely not.

Q. Is that an accepted scientific consensus?

S. HECHT

A. Yes. It is rock solid.

Q. I want to ask one other question. If you have explained it as part of your description, you can just confirm that, but I want to make sure for the transcript, you mentioned alkylation, what does that specifically mean?

A. That is the process by which either the methyl group from dimethylnitrosamine or the ethyl group from diethylnitrosamine becomes attached to the guanine that is in DNA, specifically to the O6 position, actually, to multiple positions on the guanine, but the O6 is the one that leads to miscoding. It leads to the GC to AT mutation.

We know this from experiments that have specifically put the methyl group on the O6 position, a single guanine in a chain of nucleotides, and then examined what the consequences were.

Q. What you just described, is that or is that not well established in the peer-reviewed literature and in the

S. HECHT

scientific consensus in the scientific community?

MR. FOWLER: Objection, form.

A. It is absolutely well established.

Q. Looking further down, about five lines up, where the authors of this study, Dr. Johnson and others, say "We calculated permissible daily exposures (PDE) for NDMA and NDEA using published rodent cancer bioassay and in vivo mutagenicity data to determine benchmark dose values and define points of departure and adjusted with appropriate uncertainty factors (UFs)."

Do you see where I just read?

A. Yes.

Q. So when the authors refer to using published rodent cancer bioassay and in vivo mutagenicity data, what does that mean?

A. The rodent bioassay data would be the large study that was discussed yesterday by Peto, Grasso, and others, on

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thousands of rats, a dose-response study. That wasn't the first study of dimethylnitrosamine carcinogenicity. The first study was back in 1956 by Magee and Barnes but that only used one dose. But there have been many subsequent studies, the largest of which was the one we discussed yesterday, which took the dose-response down to extremely low doses, and that's what they used in this calculation.

Q. So based on what this -- rephrase.

So based on what I just read and what you just discussed, am I correct that this study utilized rodent data to establish its proposed permissible daily exposures and the FDA also used rodent data to utilize its model to establish the acceptable intake levels that actually apply in the United States, do I understand that correctly?

MR. FOWLER: Objection to form, leading, mischaracterizes.

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A. Yes.

Q. And at the very bottom of this page it says PDEs, permissible daily exposures, for NDMA were 6.2 and 0.6 UG per person per day for cancer and mutation.

What I will focus on is the higher level, the 6.2 micrograms would convert to nanograms by just multiplying by 1,000, that would take us to 6,200 nanograms, correct?

A. Yes.

Q. And without going back to your report which documents the levels that you relied on based on what we learned in discovery, did you note that the ZHP levels certainly exceed and in many cases far exceed that level of NDMA?

MR. FOWLER: Objection, form, leading, facts not in evidence, mischaracterizes the facts. Go ahead.

A. Yes.

MR. SLATER: Chris, could you scroll down now so we can just get the carry-over of the abstract. Perfect.

S. HECHT

Q. This also provides the levels for NDEA, and those are stated as 2.2 and 0.04, correct?

A. Yes.

Q. Now, these levels are higher than the acceptable intake levels that the FDA has established in the United States, correct?

MR. FOWLER: Objection, form, leading.

A. Well, the 96 nanograms I believe was for NDMA.

Q. And the 26.5 for NDEA?

A. Okay, the 26.5, all right, yes, there are.

Q. And I will ask it again, just clean.

Are these proposed permissible exposure levels in excess of what the FDA set? And you can see the FDA levels are right there in the next sentence.

MR. FOWLER: Objection to form.

A. Yes.

MR. FOWLER: Leading. You have

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to pause.

Q. I will ask it differently.

A. Yeah, it says right here they are higher.

Q. It says "Both PDEs are higher than the acceptable daily intake values (96 nanograms for NDMA and 26.5 nanograms for NDEA) calculated by regulatory authorities using simple linear extrapolation from carcinogenicity data."

That's what the authors disclose here, correct?

A. Yes.

MR. FOWLER: Objection to form, leading.

Q. And I understand you said yesterday your opinion is that no level should be acceptable for NDMA and NDEA because it is feasible to keep it out of the pills, but if you had to choose between the FDA level and the levels proposed here, which level would you in your opinion believe is more reasonable?

MR. FOWLER: Objection, form,

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leading, mischaracterizing, incomplete hypothetical. Go ahead.

A. I don't think -- I wouldn't want to take a pill with any NDMA or NDEA in it. I think it is a failure of chemistry and manufacturing. The level should be zero. That's my opinion.

Q. If you were forced to choose between the FDA levels and the proposed levels here, which would you select if that was your only two choices?

MR. FOWLER: Objection, form, improper. Are you asking him what medicine he would take, Counsel? Is that your question?

MR. SLATER: No, I'm sorry, don't be angry.

MR. FOWLER: I just can't fathom what you are asking.

MR. SLATER: Sure, I will ask it more clearly, because it was a long night last night, but I will ask it again.

Q. Doctor, if you -- rephrase.

In your opinion, if the only

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choice for the acceptable levels for NDMA and NDEA in drugs in the United States, if one choice was the level set by the FDA, 96 nanograms for NDMA and 26.5 nanograms for NDEA, if that was one choice and if on the other hand it was the levels that Dr. Johnson suggests of 6,200 nanograms per day of NDMA and 2,200 nanograms per day of NDEA, which would you choose, if those were your only choices in that hypothetical?

MR. FOWLER: Same objection.

A. I would go with the FDA.

Q. Let's go now --

MR. SLATER: You can take that down, Chris, please.

Q. Dr. Hecht, would you please turn to page 25 of your report.

A. Okay.

Q. I'm looking in the center of your report -- rephrase.

I'm looking at the center of page 25, heading 5 says Nitrosamines in the Finished Dose Formulations. I'm going to read something and then I'm going to ask

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you a question, okay?

This says "The NDMA and NDEA levels would be expected to be the same or nearly so in the finished dose formulations incorporating the contaminated valsartan API. This was addressed and confirmed in the deposition of Hai Wang, the president of Solco, ZHP's wholly-owned distributor in the United States. Hai Wang confirmed that this was determined by ZHP and that data was provided to the FDA."

Do you see what I just read?

A. Yeah.

MR. FOWLER: Objection, form, leading.

Q. And did you rely on that testimony by Hai Wang, the president of Solco, in forming your opinions in this case?

A. Yes.

Q. Let's go now to the next page, which is the carry-over from Section 6 which is titled Nitrosamines in the Teva Finished Dose Formulation. At the top of

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page 26, the carry-over paragraph, there is a sentence that states "Daniel Barreto, Teva's former Senior Vice President Global Quality Compliance, testified that the finished dose product would have the same levels of NDMA as tested in the API and Teva extrapolated the nitrosamine test results of the API to the valsartan finished dose."

Did you rely on that testimony as well in forming your opinions?

A. Yes.

MR. FOWLER: Objection, form, mischaracterizing, leading.

MR. SLATER: Chris, could you please put up the summary of the FDA public workshop that Dr. Hecht was asked about yesterday, please. Just for the record, do we know what exhibit this was marked as yesterday?

MR. FOWLER: I believe it was 13, Counsel.

MR. SLATER: Great, thank you.

Q. This is titled Nitrosamines as

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Impurities in Drugs, Health Risk Assessment and Mitigation Public Workshop, March 29 to 30, 2021, and it was offered by the Office of New Drugs, Food and Drug Administration, and that was the workshop that you participated in and were questioned about yesterday, correct, Dr. Hecht?

A. Yes.

MR. SLATER: Chris, please go to page 1, the very beginning. Perfect.

Q. This states at the very beginning "Purpose and goals of the workshop. The Office of New Drugs in the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) organized this public workshop. International and national experts on nitrosamines were invited to discuss the chemistry and toxicology of nitrosamines in the environment and those recently identified as contaminants in pharmaceuticals."

I want to stop there. Doctor, were you one of those experts that was

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invited by the FDA to participate in this workshop?

A. Yes.

MR. FOWLER: Objection to form.

A. Yes, I was.

MR. SLATER: Chris, please go to page 4, if you could. Actually, let me see if I can find something. One second. Just bear with me for one second. I'm trying to figure out how to minimize my Zoom screen. Here it is. And it is not letting me do it. That's not good.

THE VIDEOGRAPHER: Counsel, if I could help you out, if you just double click on the screen it should minimize it I think for you.

MR. SLATER: Beautiful, thank you very much. I appreciate it.

THE VIDEOGRAPHER: Yeah, no worries.

MR. SLATER: Okay, let's go now, Chris, to page 4, and focus on the very bottom of the page, the last paragraph, or last section.

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Q. Doctor, you were asked a bunch of questions yesterday about what you said and what this group concluded regarding endogenous NDMA formation and the levels thereof. Do you recall you were asked about that a bit yesterday?

A. Yes.

Q. I'm going to go through this document a bit and walk through some of the language. At the bottom of page 4, it says "In addition to their abundance in the environment, nitrosamines are formed endogenously. To calculate risk, it is imperative to determine endogenous formation and understand the pharmacokinetics of nitrosamine formation and distribution. At this time there is a considerable gap in knowledge on the endogenous formation of nitrosamines in general, and NDMA in particular. It is unknown whether endogenous formation of carcinogenic nitrosamines exceeds, is equal to, or is less than, the levels detected in pharmaceuticals."

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Do you see what I just read?

A. Yes.

Q. Do you agree with that statement?

A. Absolutely.

Q. Let's go now to page 5, and let's go to the third full paragraph. The third full paragraph on page 5 says "However, reliable data on many reactive carcinogenic nitrosamines, for example, NDMA and NDEA, are sparse because they are rapidly metabolized and the distribution and excretion of their metabolites are unclear."

I want to stop there, Doctor. Can you explain what that means, what I just read, that sentence, please?

MR. FOWLER: Objection, leading, mischaracterizing.

A. It means exactly what it says, the NDMA and NDEA are rapidly metabolized by cytochrome P450 in the liver and other tissues, and the metabolites are very short-lived, and, you know, the

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distribution and excretion of the metabolites is unclear. I mean, I don't know how else to say it.

Q. In the beginning it refers to reactive carcinogenic nitrosamines and gives examples of NDMA and NDEA. What is a reactive carcinogenic nitrosamine?

A. So what they are saying here is that NDMA and NDEA, when metabolized, become extremely unstable and give rise to reactive intermediates. That's what they -- that's what they are trying to say.

NDMA and NDEA themselves are actually stable compounds. They are not terribly reactive, but when they interact with P450s in the body, which happens mainly in the liver, but also in other tissues, they are converted to extremely reactive intermediates, formaldehyde and methyldiazohydroxyl.

Q. Continuing to read this paragraph --

A. So there is no --

Q. I'm sorry, go ahead.

S. HECHT

A. There is no characteristic NDMA metabolite that is excreted in the urine that you can really use to monitor its dose even.

Q. If I continue to read now, the second sentence of this paragraph says "It is assumed however, that NDMA and NDEA are formed endogenously as their dietary precursors (dimethylamine and diethylamine, respectively), which, together with nitrites and nitrates, are present in foods. However, no quantitative assessment of NDMA or NDEA is available because of their rapid metabolism."

Focusing on that last sentence along with the first sentence we went through, is that consistent with your opinion?

MR. FOWLER: Objection, leading.

A. No, it is absolutely right. I mean, we just don't know about endogenous formation of NDMA and NDEA. I mean, you can contrast it to nitrosoproline which is

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unmetabolized, excreted 100 percent unchanged, because of its high polarity.

So nitrosoproline is a great monitor for endogenous formation. You can give proline to people and measure the nitrosoproline, the increase in nitrosoproline, that is excreted in urine, in people who were exposed, for example, to nitrite. It is a great monitor of endogenous formation, but you can't do that with NDMA and NDEA because they are rapidly metabolized and their metabolites cannot easily be quantified. So we don't know.

MR. SLATER: Chris, please scroll down to page 14, please, the last paragraph.

Q. Looking now at page 14, at the bottom, the last paragraph is a paragraph you were specifically asked about yesterday, and I want to walk through the whole paragraph though, rather than just the one sentence that was focused on.

Looking now, new question, looking now at page 14, the last paragraph,

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this states "The need for up-to-date information on exogenous and endogenous formation of nitrosamines was reiterated by the expert panelists. Such information is essential for risk assessment and accurate calculation of acceptable intake. However, most available data are 20 to 50 years old and much has changed since, including dietary habits, exposures, and analytical methods."

The next sentence says "The levels of nitrosamines as impurities in drugs are likely minuscule in comparison to exogenous exposure from foods and even more so to endogenous levels."

Do you recall you were asked about that sentence and the suggestion that the levels are minuscule?

MR. FOWLER: Objection to form.

Q. In drugs as compared to exogenous and then, more so, endogenous levels, do you remember you were asked about that yesterday?

A. Yes, I do remember.

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MR. FOWLER: Objection to form.
Q. Let's look at the next sentence which you were not asked about yesterday. The next sentence, after what you were asked, says "However, this estimate is based on old data and is thus likely to be inaccurate."
I want to stop there. Do you agree with that statement?
MR. FOWLER: Objection.
A. That's what I said yesterday. We don't know, and the data that's out there is questionable. I said that yesterday.
Q. Continuing, the paragraph says "By contrast, data on nitrosamines in food are more up-to-date and the food industry has made much improvement over the past few decades.
A. Absolutely.
Q. When this talks about the food industry making improvement, what is that referring to?
A. Well, they made process changes

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having to do with the composition of foods and the storage of foods. It is also -- it is also true for beer, in the whole manufacturing process to minimize the chance of nitrosamine formation by removing the precursors or by using inhibitors of the reaction, for example, ascorbic acid is known to inhibit nitrosation, and lowering the nitrite content, for example, in cured meats.
I mean, so there are a lot of process changes that have occurred over, well, since the '70s, over the last 50 years. So really the levels of nitrosamines in food now are quite low. They typically don't exceed 10 parts per billion, or even lower.
Q. Thank you.
MR. SLATER: Chris, you can take that down. Let's go now to the transcript of the workshop, day one, page 61, please. If you can blow that up a little bit just so that it is easier to read for everybody. Terrific.

S. HECHT
Q. Starting from the top, and when I get to the point where you need to scroll, you can just scroll with me. Dr. Hecht, this is the transcript of a portion of that workshop, and you can see at the top of page 61 there is something that you stated, because we can see "Dr. Hecht," so this is you speaking, correct?
A. Yes.
Q. And I'm going to read what you said and then ask you a question about it.
You said "Yes, so, we know quite a bit about endogenous formation based on studies that have been carried out with nitrosoproline where subjects have been dosed with proline plus nitrite or even proline plus nitrate, and then nitrosoproline can be quantified in the urine because nitrosoproline is not metabolized. It is also not carcinogenic. So, many studies on nitrosoproline formation have been carried out, which demonstrate the endogenous formation of

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nitrosamine. So, the overall yield is actually quite low based on the amounts of proline and nitrate that are given. But we do not have reliable data for compounds such as dimethylnitrosamine because dimethylnitrosamine is rapidly metabolized in the liver, and we do not have good data on the quantitative formation and excretion of its metabolites."
So I want to stop there. Is that consistent with what your opinion has been throughout, and does this now show this is what you actually stated during the FDA workshop?
A. Yes.
MR. FOWLER: Objection, leading.
A. That is what I said, that is what I believe, and, you know, that's the truth. So I don't know what some of these other statements yesterday were all about. This is what I said and this is what I believe.
Q. Is that -- rephrase.

S. HECHT

The statements that you made that we just read and the parts of the FDA workshop report or summary report that we went through before regarding the data on endogenous formation of nitrosamines, do you believe that that is scientifically accepted among those people who study these issues?

MR. FOWLER: Objection, leading.

A. Do I believe that --

Q. That those concepts --

A. -- what I said here is accepted?

Q. Yes.

A. Yes, absolutely.

MR. SLATER: Okay, we can take that transcript down. And the next thing I would like to look to is the Knekt article that Dr. Hecht was asked about yesterday, spend a moment on that. If you can blow up the abstract, Chris, that would be great, because I think we can just work off that for ease of reference and to be a little

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more efficient. I think that's good.

Q. In the middle of the abstract, this study says "A significant positive association was observed between intake of NDMA and subsequent occurrence of colorectal cancer with a relative risk (RR) between the highest and lowest quartiles of intake of 2.12 (95 percent confidence interval (CI) 1.04 to 4.33)."

Do you see what I just read, Doctor?

MR. FOWLER: Objection, leading.

A. Yes.

Q. What does that mean, what does that statement that I just read mean?

A. It means the relative risk for colorectal cancer is 2.12, so if the CI, 95 percent confidence interval, if it is greater than 1, then it is statistically significant, so, you know, the 1.04 to 4.33 indicates that this 2.12 is statistically significant, so it means a higher relative risk, for the highest versus the lowest

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intake of NDMA and occurrence of colorectal cancer. It is a significant one.

Q. And in order to give a little bit of a snapshot of your methodology and your thinking on this, was that significant to you in your overall analysis of the weight of the evidence in this matter?

A. Yes.

MR. FOWLER: Objection, leading.

Q. And can you explain how it is that you incorporated that information into your overall analysis? How did it fit?

MR. FOWLER: Objection, leading, mischaracterizes, facts not in evidence.

A. Well, it is part of the -- it is one of the studies of NDMA exposure through foods and cancer that gave a positive result, and, you know, this study was strong because it was a cohort study, nearly 10,000 adults, and in a cohort study it is a strong design because you follow the cohort for years and you have -- and

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you obtain information on their diet and from this dietary information tables that are available for analysis of various compounds, including nitrosamines, in the diet, you can calculate the intake and then you can follow the people for years. So there is no chance of recall bias that is a problem in case control studies.

So you follow them for years and then you compare the incidence of cancer to the dietary data. That's what they did here. So it is a strong study design, it is a large study, and they have good, solid data.

Q. And to be fair, further down, it says "No significant associations were observed between NDMA intake and cancers of the head and neck combined or of the stomach or between nitrate or nitrite intake and risk of cancers of the gastrointestinal tract."

Do you see that?

A. Yup.

Q. Is that something you also

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considered as part of your analysis of the weight of the evidence here?

A. Yes.

MR. FOWLER: Objection, leading.

A. Yes.

Q. And can you explain how that fit into your analysis as well, how you took that into account, these negative findings?

MR. FOWLER: Objection, leading, lack of foundation.

A. It is logical because we know from animal studies that nitrate and nitrite don't cause cancer, but NDMA does, so it is logical.

Q. And the part where --

A. It is consistent with the animal studies.

Q. And where this says that "No significant associations were observed between NDMA intake and cancers of the head and neck combined or of the stomach," I will stop there, just talking about the

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NDMA, how did you take that negative finding into account as part of your analysis of the weight of evidence?

MR. FOWLER: Objection, leading, lack of foundation.

A. Well, they just didn't -- they just did not see a positive association for these other two tumor types, and this is really not that surprising because, I mean, there is no animal data that indicates that NDMA causes stomach cancer, and in general it doesn't cause head and neck cancer either.

Q. If someone were to suggest that in the absence of fully consistent data in all of these studies showing significant positive associations between NDMA and cancer that you shouldn't be able to give the opinion you have given about the risk, the increased risk of cancer from NDMA intake, what would be your response to that, someone saying you have to have uniform findings of significant association across all studies, what would be your

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response to that?

MR. FOWLER: Objection, leading, incomplete hypothetical, foundation, speculation, probably more. Go ahead.

A. Could you repeat the question?

Q. Hopefully not, because it sounded like there are a lot of objections to it, so it probably wasn't a good question.

Is uniform results of a statistically significant positive association to cancer necessary in order for you to form your opinion, and can you explain your answer?

MR. FOWLER: Objection.

Q. Across all studies.

A. You know, these studies are challenging to do. There are a lot of design aspects, you know, you are following people for years, and so, you know, there is a lot of potential variability. They are really -- they are really very challenging studies to do. So, you know,

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when you have these cohort studies that are showing a positive result and that positive result is consistent with what we know from experimental studies in animals, it is very compelling.

Q. So to be clear, did you include in your analysis of the weight of the evidence the findings in the studies of positive associations, those that were strong, those that were weak, and those where no association was found, did you take all of that into account across the board?

MR. FOWLER: Objection, leading.

A. Yes.

Q. And we are going to get to this a little more later, but I want to ask one question.

Did you also look at this study and other studies that you looked at in the context of the animal studies and the mechanistic evidence as well so that you were looking at things together as part of

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your weight of evidence analysis?

A. Yes.

MR. FOWLER: Objection, leading, foundation. Doctor, you have to give me a second, we are stepping on each other, please.

MR. SLATER: And let's turn now, if we could, to page 854, please, Chris, the Discussion paragraph, lower left. Perfect. If you could blow up that paragraph. Thank you very much.

Q. In the Discussion, the first sentence says, looking now at page 854, the Discussion section of the article, it says "In the present cohort study, we found an increased risk of colorectal cancer among individuals with a high intake of NDMA."

That is ultimately their ultimate conclusion, correct?

MR. FOWLER: Objection, leading.

Q. With regard to colorectal cancer.

MR. FOWLER: Same objection.

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A. Yes.

Q. If we go down a little further, I want to read something and ask you a question about it.

It says "Nitrosamines are potent carcinogens and NDMA has been shown to induce formation of DNA adducts in human colonocytes which may behave as an initiator of carcinogenesis."

What does that statement mean?

MR. FOWLER: Objection, leading.

A. They did organ culture studies, in vitro studies with human colonocytes, Autrup did that in the '70s by incubating the colonocytes with NDMA, and then they isolated DNA from the colonocytes and analyzed for O6-methylguanine and other DNA, I guess 7-methylguanine, and, you know, they got a positive result.

So that was compared to a control, you know, where you have NDMA with colonocytes that have been killed so that there is no metabolism or simply the

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colonocytes without the NDMA.

Q. Is that --

A. Very convincing data. I mean, by current-day standards, the techniques were a little different, but the result is the same.

Q. Is that significant to you in your reaching your opinions here in this matter?

MR. FOWLER: Objection.

A. I mean, the human metabolism of nitrosamines study by Autrup and Harris and others in the late 1970s was very significant because it showed that human tissues could metabolize nitrosamines. I mean, that wasn't known before then, because all the studies had been done in rats, so as we discussed repeatedly during these sessions, metabolism is absolutely required for the carcinogenicity of dimethylnitrosamine. These studies demonstrated that clearly back in the '70s, and everything that has been done since then is consistent with that.

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Q. And why is that important to you -- rephrase.

Why is that significant to you in forming your opinion that NDMA and NDEA are human carcinogens?

MR. FOWLER: Objection, leading, lack of foundation.

A. Because here they used human tissues to show that human tissues were capable of metabolizing NDMA and NDEA. As we said before, metabolism is required for the carcinogenicity of NDMA, and so, you know, at that time questions still existed whether human tissues could metabolize NDMA, and these studies by Autrup, Harris, and others showed that they could.

Even colonocytes, that's significant with respect to this particular study by Knekt, because that's where they found the higher risk for cancer in the colon, colorectal.

Q. Thank you.

MR. SLATER: We can take that down. Chris, the next one we will go to is

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a study authored by Wang, et al.

Q. Doctor, we have put up on the screen -- I guess we will have to mark this as a deposition exhibit.

MR. SLATER: Are we up to 28, did I guess that right?

THE VIDEOGRAPHER: You are correct, 28.

MR. SLATER: Thank you.

(Hecht Exhibit 28 marked for identification.)

Q. Doctor, can you please read for us the title of this article? Because I'm not going to try to read all those words.

A. "Development of liquid chromatography electrospray ionization tandem mass spectrometry methods for analysis of DNA adducts of formaldehyde and their application to rats treated with N-nitrosodimethylamine or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone."

I wrote that title. It is a little too long, but anyhow --

S. HECHT

Q. And I see the author --

A. -- it is what it is.

Q. Looking at the authors, going by last names, Wang, Cheng, Villalta and Hecht. Is that you?

A. Yup.

Q. Before we get into a couple of specifics of this study, what generally was this study -- what was this study and why was it done?

A. So we were interested in NNK for many years, that's the last compound here, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, we call it NNK for short, and we had done many studies on DNA damage by this compound, also its metabolism and carcinogenicity.

In this study we wanted to evaluate formaldehyde release. As I mentioned yesterday, N-nitrosomethyl compounds in their metabolism in the first step will release formaldehyde, and there has been a lot of work on the methyl and other DNA damage from nitrosamines. There

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really wasn't much work on the fate of the formaldehyde that is formed. So that's what we are looking at in this study.

Q. Looking now -- if you could scroll to the bottom of the page, Chris, please -- at the very bottom right, and we are just going to go over to the next side, the article states "The methods were applied" -- rephrase, I'm going to start over.

Looking at the bottom right, it says -- rephrase.

Looking at the bottom right of the first page of the study, it says "The methods were applied for the analysis of adducts 1 and 2 in rats treated with the carcinogenic nitrosamines, N-nitrosodimethylamine (NDMA) and NNK," I'm going to go with the abbreviation, "NDMA and NNK are representative N-nitrosomethyl carcinogens."

I want to stop there. Is this a peer-reviewed article?

A. Yes.

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MR. FOWLER: Objection. You are leading the doctor through his own article.

Q. And in this peer-reviewed article, you referred to NDMA as a carcinogenic nitrosamine, correct?

A. Yes.

MR. FOWLER: Objection, leading.

Q. I'm going to continue. You state in this article "Beginning with the landmark studies of Magee, Dutton, Heath and Druckrey nearly 50 years ago, well-established pathways of metabolic activation of nitrosamines involving cytochrome P450-mediated a-methyl hydroxylation have been described in the literature."

I'm going to stop there. Is that what we have been talking about already today a little bit, how these substances are metabolized?

A. Yes.

MR. FOWLER: Objection,

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leading, foundation.

Q. I'm going to go down a little further, and at my peril I'm going to try to read -- actually, let's do it cleaner. If you go down to -- rephrase.

If you skip the next sentence after what I just read there is a sentence that starts out "These diazohydroxides," do you see that?

A. I'm having a little trouble seeing. Can you blow it up a little? I'm not sure exactly where you are.

MR. SLATER: Yeah, blow up that top paragraph, Chris, please.

A. Yeah, I can see it now.

MR. SLATER: A little more. We are only talking about that one, so if you can make that bigger, Chris, that would be great. Perfect.

Q. Is that good, Doctor?

A. Yeah.

Q. So about halfway down after the bold number 10, there is a sentence that starts "These diazohydroxides." Would you

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be so kind as to read that sentence and the next one, please, just because I'm virtually certain I will mispronounce a few of those terms.

A. "These diazohydroxides or the corresponding diazonium ions react with DNA, producing adducts such as O6-methylguanine, or dGuo, from NDMA and O6-pyridyoxobutyl dGuo (O6-POB-dGuo) from NNK. The roles in carcinogenesis of these and related methyl and pyridyoxobutyl and DNA adducts of NDMA, NNK, and other N-nitroso compounds have been extensively studied."

Q. I want to stop there. What is it that you are describing in those two sentences?

A. DNA damage by dimethylnitrosamine and NNK.

Q. Bear with me one second. I'm just going to switch to my hotspot because I'm losing my signal again. Can everyone hear me?

A. Yes.

S. HECHT

Q. Thank you. Thank you, Doctor.

At the bottom of that paragraph you state in this paper, "We present the first evidence that formaldehyde DNA adducts are formed in the lung and liver of rats treated with NDMA and NNK."

Why was that significant and why did you publish on that?

MR. FOWLER: Objection, form, foundation, leading.

A. It is important because all of the studies up until that time with NDMA and NNK, compounds like it, have focused on the methyl DNA damage that we have discussed extensively before, but, you know, the first step in the metabolism of dimethylnitrosamine that forms the methylating agent also forms formaldehyde, and the formaldehyde part of the overall picture had not been studied. So that's what we did here.

Q. And is this study and what you learned from it something you take into account in forming the opinion you have

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offered in this case?

MR. FOWLER: Objection, leading, foundation.

A. Yes.

Q. And why is that?

MR. FOWLER: Same.

A. Because the carcinogenicity of dimethylnitrosamine I believe goes beyond just O6-methylguanine, that is very important, there is no doubt about it, but there are other parts of the DNA damage picture that haven't been fully evaluated. That's what we tried to do here. That's what we started to do.

MR. SLATER: Okay. We can take that down and go to the Herron article, please. Chris, can you put up the Herron and Shank article, please.

Q. Can you hear me?

A. Yes.

Q. Great, okay. Chris is so fast usually that when it doesn't happen instantaneously I wonder if he has dropped off. I guess this is Exhibit 29 now.

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(Hecht Exhibit 29 marked for identification.)

Q. Looking at this study, it is titled "Methylated Purines in Human Liver DNA after Probable Dimethylnitrosamine Poisoning." It was published in the Journal of Cancer Research in 1980 and the authors are Herron and Shank.

Is this an article that you have taken into consideration in forming your opinions in this case?

A. Yes.

Q. And let's just set the stage, if you will.

MR. SLATER: Let's look at the abstract, please, Chris. We will just work with that in the interest of time.

Q. This says "DNA, isolated from two samples of human liver obtained from a suspected dimethylnitrosamine poisoning, contained 1,363 to 1,373 umol of 7-methylguanine per mol of guanine and 273 to 317 umol of 06-methylguanine per mol of guanine."

S. HECHT

If we go down a little further, it states "From the DNA methylation levels, it is estimated that the dimethylnitrosamine poisoning victim had been exposed to a dose of 20 milligrams or more of dimethylnitrosamine per kilogram of body weight. The results indicate for the first time that humans, like rodents, appear to activate dimethylnitrosamine metabolically to a strong methylating agent, resulting in methylation of liver DNA at both the 7- and O6 positions of guanine."

Is what I just read significant to you in forming your opinions, Doctor?

A. Yes.

MR. FOWLER: Objection, leading, foundation.

Q. Can you please tell us why?

MR. FOWLER: Same objection.

A. Yes, absolutely it is significant because it shows that in a human you are getting the same types of DNA damage from dimethylnitrosamine that you

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get in a rat. It is very significant.

MR. SLATER: Okay, let's take that down.

A. This was a human that was dosed with dimethylnitrosamine which you can't do because of its carcinogenicity, so you can't do that experiment, but this was a murder case.

MR. FOWLER: Objection, move to strike. That was a response to no question. There was no question pending. Move to strike his statement.

A. It was murder, so dimethylnitrosamine is poisonous at this dose.

MR. FOWLER: There is no question on the table.

Q. I'm sorry, thank you, Doctor, for continuing to answer, I didn't mean to interrupt you in the middle of your answer,

MR. SLATER: Let's take that down, and let's go to the Gomm study, and go to page 360, please. If you go to page 360, the bottom Biological Background

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section, please, and I'm focused on the first couple of sentences. I think we've got to get bigger and bigger. Perfect, thank you. And what was this marked as, as an exhibit yesterday, if someone could help me out? I just want to make sure the record is clean.

THE VIDEOGRAPHER: One moment, let me find it here. That was Exhibit 22.

MR. SLATER: Okay, thank you very much.

Q. Looking at the study by Gomm, et al., which is Exhibit 22 from yesterday, looking at page 360, Biological Background section, it starts "Outside NDMA is classified by the IARC as probably carcinogenic (group 2A)."

I'm going to stop there. This is a peer-reviewed article, correct?

MR. FOWLER: Objection, leading.

A. Yes.

Q. And it is citing to the IARC finding that NDMA is probably carcinogenic,

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do I read that correctly?
MR. FOWLER: Leading.
A. Yes.
Q. Looking at the second sentence under Biological Background, it states "It is carcinogenic in the tissues of experimental animal species with metabolism similar to that of human tissues."
I know we have been over this a bit, but can you just explain to us why, if at all, that is significant and how it fits your analysis here?
MR. FOWLER: Objection, leading, foundation.
A. NDMA requires metabolism in order to be carcinogenic. Without metabolism, there would be no effect, because metabolism produces the intermediates that damage DNA. So in the previous paper that we discussed, Herron and Shank showed that humans metabolize NDMA to these DNA adducts the same way rats do.
MR. SLATER: Chris, could you

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go up to the top right carry-over paragraph, please, and we are going to go to the bottom part of that. Perfect.
Q. Looking at the carry-over paragraph from where we were just reading, the bottom of that carry-over paragraph in the top right says "The effect of NDMA exposure on liver cancer is a statistical result. However, molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans."
What is that telling us?
MR. FOWLER: Objection, leading, foundation, speculation.
A. He is saying basically that the similarities between metabolism and DNA damage, in other words, the mechanism of NDMA carcinogenesis that's been so well delineated in laboratory animals and by molecular biology techniques is consistent with everything we see in humans, for example, the Herron and Shank study, and there are other studies as well, Autrup and

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all the others we have been talking about. So he is saying that the human mechanistic data is completely consistent with the animal data.
MR. SLATER: Could you scroll down a little bit, Chris, to the next section in the middle of the page right there. Perfect.
Q. There is a heading Regulatory and Public Health Implications on the right-hand side of page 360, and I want to read a sentence and ask you a question. It says, halfway down, "The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities worldwide was necessary in order to protect public health."
I want to stop there. Is that decision that was made worldwide as stated, how does that relate, if at all, to your opinion as to the human carcinogenicity of NDMA and NDEA?
MR. FOWLER: Objection, leading, lack of foundation,

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mischaracterizes.
A. It was absolutely necessary to protect human health, as I've said many times. I mean, there is no -- there is no way that these valsartan tablets should have been contaminated with dimethylnitrosamine. That's a horrible outcome. It never should have happened. All of that should have been taken off the market.
Q. When they refer --
MR. FOWLER: Move to strike, beyond the scope of the proffer agreed to by counsel not to get into liability issues, which is exactly what you're doing, Counsel.
Q. With regard to the phrase of protecting the public health, tell me if I understand this, protecting the public health is because these substances, NDMA and NDEA, were considered to be so dangerous to humans, especially at the levels from the regulatory perspective, especially at the levels that they

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contained -- let me rephrase. I'm going to withdraw the question.

With regard to the need to protect public health as stated in this article, was that due to the fact that it was understood that it was too dangerous to humans to have those substances in those pills and have them ingested by humans, is that consistent or not consistent with your understanding?

MR. FOWLER: Objection, foundation, calls for speculation, mischaracterizing. Go ahead, Doctor.

A. That's what he is talking about.

Q. Let's go down a little bit further into the Conclusion at the bottom of the page. Perfect. About a little past halfway down the Conclusion, there is a sentence that says "Long-term effects of regular use of potentially NDMA-contaminated valsartan for more than 3 years could not be evaluated because of the currently still relatively short follow-up

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time."

And with regard to that, what from your perspective is the significance of the fact that this was not able to evaluate long-term effects just because only a few years had passed since this was discovered by people in the world?

MR. FOWLER: Objection.

Q. Let me rephrase it. I have to rephrase the question actually, sorry, Doctor. That was not artful, so I'm going to ask it again.

In the conclusion at the bottom right of page 360 it states "Long-term effects of regular use of potentially NDMA-contaminated valsartan for more than 3 years could not be evaluated because of the currently still relatively short follow-up time."

Is that significant to you in your evaluation of this study and the data?

MR. FOWLER: Objection, leading, foundation.

A. Yes.

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Q. Why?

MR. FOWLER: Same objection.

A. Well, they haven't been exposed for a very long period of time to the contaminated valsartan. I mean, you would expect that the effect would increase with time, with longer exposure. I mean, that's just simple dose-response.

Q. When they refer to the relatively short follow-up time, what are they referring to?

MR. FOWLER: Objection, leading, speculation, foundation.

A. The three years. You know, they are referring to the relatively short time that these contaminated pills have been out there.

Q. Are they also referring to the fact that from the time of discovery in 2018 to the time of publication of this study there was a relatively short follow-up time to see what the long-term effect is so they can't study the long-term effects yet?

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MR. FOWLER: Objection, leading, asked and answered.

A. Yes.

MR. FOWLER: Leading.

A. Yes.

THE VIDEOGRAPHER: Counsel, sorry to cut in, I just want to let you know, I have about ten minutes on this media before I will need a quick break.

MR. SLATER: Fine.

Q. Ultimately, with regard to what is referred to as the short follow-up time, from your perspective, would it be prudent to continue to follow people going forward to get longer-term data on the impact of this exposure?

A. Yes.

MR. FOWLER: Objection, leading, beyond the scope.

A. Absolutely.

Q. Why is that?

MR. FOWLER: Same.

A. Pardon?

Q. Why is that?

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MR. FOWLER: Calls for speculation.

A. Well, you would expect, you know, if this effect that they are seeing is real, after only three years of follow-up, you would expect an increase with, you know, longer use of the contaminated pills and as well as the longer period for liver cancer to develop, if that's what's going on. So definitely, you know, there should be longer follow-up.

MR. SLATER: Can you go back to page 359, please, Chris, the top left of the page. Perfect.

Q. The top left of page 359, it says "Comparison with other studies on valsartan exposure." It says "Only one cohort study on this topic has been published to date; the Danish registry study by Pottegard, et al., has only a small sample size, comprising 5,150 persons with prescription of valsartan. Our study contains around 150 times more persons with valsartan prescription."

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I would like to stop there. Is that significant to you in evaluating this study and the Pottegard study?

MR. FOWLER: Objection, leading, lack of foundation.

A. Yes, sure.

Q. Why is that?

A. Well, you need the big numbers to detect what might be, you know, a relatively small percentage of people who are going to be affected. So you need big numbers for a study like this.

MR. SLATER: And let's go to the -- let's take this down and go to the Pottegard study, please. Actually, before we start that, do you want to just flip your tape? This should only take a second, right?

THE VIDEOGRAPHER: Yeah, only about 30 seconds.

MR. SLATER: Okay, let's do that.

THE VIDEOGRAPHER: The time is 10:31. This concludes media one.

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(Recess taken.)

THE VIDEOGRAPHER: The time is now 10:32. This begins media two.

BY MR. SLATER:

Q. Doctor, we have up on the screen the Pottegard study.

MR. SLATER: And I'm just, for the record, again, could somebody tell me, please, what exhibit number this is, just so we have that? I think it is 10.

THE VIDEOGRAPHER: This is Exhibit 21.

MR. SLATER: Got that wrong, okay.

Q. Looking at Exhibit 21, the Pottegard study, let's go, if we could, to page 2, and I want to look at the section titled Study Cohort, please. Perfect. This says "The study cohort comprised all Danish patients filling a valsartan prescription during the study period of 1 January 2012 to 30 June 2018. Prevalent users of valsartan at the start of the study period - defined as individuals

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having filled a valsartan prescription in September to the end of December 2011, entered the study cohort at 1 January 2012, whereas incident users entered the study cohort at the day of filling their first valsartan prescription during the study period."

So this is helping to define who are the people being studied, do I understand that correctly?

MR. FOWLER: Objection, leading.

A. Yes.

Q. Let's go to the bottom of the page, please, where there is a heading that says Ascertainment of NDMA Exposure. It says "Within the study cohort we mapped out each participant's exposure to NDMA contamination using the unique drug ID (Nordic article number) as recorded in the National Prescription Registry to identify the single valsartan product and its manufacturer."

Going a little -- rephrase.

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It continues, "From the 128 unique valsartan drug products used during 2012 to 2018 within our study population, we identified 18 drug products (which constituted 18 percent of all prescriptions filled) that were manufactured using an active pharmaceutical ingredient from ZHP, Zhejiang Huahai Pharmaceuticals. These drug products were classified as probably contaminated with NDMA. An additional 36 drug products (26 percent of all prescriptions) were classified as possibly contaminated with NDMA" -- you can go up to the top of the next column, please -- "as they contained an active pharmaceutical ingredient both from Zhejiang Huahai Pharmaceuticals and from other companies. 74 drug products (55 percent of all prescriptions) were classified as unlikely to be contaminated with NDMA as they did not contain an active pharmaceutical ingredient from ZHP."

I will stop there. So if I understand correctly, the cohorts are

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people who were exposed to ZHP valsartan API and those that were not, do I understand that correctly?

MR. FOWLER: Objection, form, leading, lack of foundation, beyond the general causation purpose of this deposition.

A. Yes.

Q. And just tell me if I'm wrong or right -- well, rephrase.

As we know from the case, other manufacturers besides ZHP also manufactured valsartan contaminated with NDMA and NDEA, we know that, correct?

A. Yes.

MR. FOWLER: Objection, leading, facts not in evidence, foundation.

Q. What, if any, significance do you attribute to the fact that the control group that was supposed to have not been exposed to contaminated NDMA included people who took pills potentially from other manufacturers other than ZHP that also manufactured contaminated valsartan,

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is that significant to you?

MR. FOWLER: Objection, leading, speculation, lack of foundation, probably others.

A. Well, then it wouldn't be a control group.

Q. Why is that?

A. Well, if they were exposed to pills that contained NDMA, then you are not comparing exposed to nonexposed, so that wouldn't be a proper control group.

Q. In terms of study design, what, if any, significance do you attribute to the fact that people in the so-called control group may have taken contaminated ZHP -- rephrase.

What, if any, significance do you attribute to the fact that the so-called control group included people who may have taken contaminated valsartan and that wasn't factored in, is that significant or not and why?

MR. FOWLER: Objection, leading, lack of foundation.

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A. It could be very significant.

Q. Why is that?

MR. FOWLER: Same objection.

A. Well, if the control group was taking contaminated tablets, then you are comparing -- your comparison is invalid.

Q. And the fact that this article --

A. Because both groups would be exposed.

Q. And the fact this article doesn't provide any certainty at all as to whether or not the control group contained people who took contaminated valsartan or how many or to what extent, how does that impact your evaluation of the data?

MR. FOWLER: Objection, leading, lack of foundation.

A. Well, if the control group was taking contaminated pills, then, you know, that invalidates the study, because you are not comparing exposed versus nonexposed.

Q. And the fact that we have no way of knowing to what extent that

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occurred, is that significant to you in evaluating the data and what weight you give to the data?

A. Yes.

MR. FOWLER: Objection, leading, speculation, foundation.

Q. And why is that?

MR. FOWLER: Same.

A. Well, if we don't know whether the control group was exposed or not, it is hard to evaluate the study. If the control group is exposed, possibly to the same extent as the treated group or the group that took the contaminated pills, then it's not a good comparison.

MR. SLATER: Okay, we can take that down.

A. It is not a valid comparison.

MR. SLATER: You can take the article down now, Chris. Thank you.

Q. Doctor, you were asked some questions yesterday about your invoices and which entries said literature search and which didn't. Do you remember you were

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asked a little about that?

A. Uh-huh.

Q. When you sent me invoices to be paid for the time you were spending in this case, were you seeking to be all encompassing as to every single thing you did during each time block that you recorded on those invoices?

MR. FOWLER: Objection, leading.

A. What do you mean by all encompassing?

MR. FOWLER: Thank you.

Q. I will ask it a little differently.

A. I gave you my best estimate of the time that I spent working on the case.

Q. Right. If you did a literature search, did you make sure that you wrote it down every single time or did you just generally summarize the work you did?

MR. FOWLER: Objection, leading.

A. I did not keep that kind of

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record.

Q. Is there any doubt that you performed an extensive literature search as you described yesterday?

MR. FOWLER: Objection, leading.

A. No, there is no doubt.

Q. You were asked yesterday something, and I want to just make sure we clarify some language, you were asked a question along the lines of whether or not it has been proven that NDMA and NDEA cause cancer in humans. Do you remember some questions along those lines?

A. I don't remember.

Q. Okay. In order to prove 100 percent or close to it, would you have to set up a study where you deliberately give these substances to humans and then have an unexposed control group and compare the effects, right?

MR. FOWLER: Objection, leading, incomplete hypothetical, speculation.

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A. Yes, that would be the ideal design.

Q. Why aren't people performing studies right now where they are giving NDMA and NDEA to human beings at the levels seen in the valsartan pills at issue in this case and letting those people be compared to people who don't get exposed, why aren't those studies being done?

MR. FOWLER: Objection, speculation.

A. That would never pass through an institutional review board. You can't give known carcinogens to subjects in a study. It would never be approved.

Q. Based on your understanding of the scientific consensus on this issue, can you envision any institution in the United States that would sponsor or permit such a study?

MR. FOWLER: Objection, leading, foundation, speculation.

A. It is absolutely impossible. It would never happen in this country,

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probably anywhere in the world.

Q. And in that context, I would like to talk about the time when these pills were being sold, before it had been disclosed that there was NDMA and NDEA contaminating the substances. I want to look back at that time period, okay?

A. Uh-huh.

Q. Based on your knowledge of everything that you have read and your familiarity with this subject matter, can you envision any circumstance where the levels of NDMA and NDEA that have been found in these pills would have been approved for sale to humans?

MR. FOWLER: Objection, form, speculation, well beyond the scope of this general causation deposition, and contrary to counsel's agreement not to get into this.

Q. You can answer.

A. No.

Q. And is that because of what you have described, the risk that people that

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would take this would get cancer as a result?

MR. FOWLER: Objection, leading, foundation, speculation.

Q. Let me ask it differently. Let me ask the question differently.

Why is that?

MR. FOWLER: Same objection.

A. They are contaminated with a carcinogen.

Q. And these pills are hypertension medications. Were they intended for short or long-term use in general?

A. Long-term use.

MR. SLATER: Let's go, if we could, Chris, to the World Health Organization publication from 2002. And let's go, if we could, to page -- well, actually let's start here on the cover, let's go on the cover, I'm sorry. And this will be Exhibit 29, I believe, right?

THE VIDEOGRAPHER: This will be 30.

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MR. SLATER: I was on a run too. Okay.

(Hecht Exhibit 30 marked for identification.)

Q. Looking at Exhibit 30, this is a document from the World Health Organization published in 2002 titled Concise International Chemical Assessment Document 38, N-nitrosodimethylamine.

Doctor, what is the World Health Organization?

A. The World Health Organization is a branch of the United Nations that evaluates and recommends policies having to do with health in the world.

Q. And this is a peer-reviewed publication, correct?

A. Yes.

Q. Let's go now, if we could, to page 23, in the interest of time. If we could, let's look at the left-hand side, and let's go to the first full paragraph that starts "With the exception of." If you could blow up that part, that would be

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great. Great, thank you.

Looking now at a portion of this publication, and we are not going to have to turn back to it, but this is the section titled Effects Evaluation, which is Section 11, Evaluation of Health Effects is 11.1, and this is the Hazard Identification section.

Here we see, on the first full paragraph on the left, the second sentence, it says "The weight of evidence of the carcinogenicity of NDMA in mammalian species is consistent and convincing. Moreover, the pattern of tumor development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material."

What I just read, is that something you agree with?

A. Yes.

MR. FOWLER: Objection, leading.

A. Yes, it's true.

Q. And in terms of the pattern of

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tumor development, in simple terms, what does that mean, just so we can orient ourselves?

A. I'm sorry, but I lost --

Q. You lost the place?

A. Yeah.

Q. It is about --

A. Where are you?

Q. It is about seven lines down. I will start over. Seven lines down is a sentence that says "Moreover, the pattern of tumor development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material."

What is that telling you?

MR. FOWLER: Objection, foundation, calls for speculation, leading.

A. It is the basic mechanism that's common to well-established carcinogens, that they are metabolically activated in tissues having the requisite enzymes and reactive intermediates are formed which then damage DNA, leading to

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mutations, everything we have been talking about for the last two days.

MR. SLATER: Let's go down to the next paragraph, Chris, please.

Q. The second to last full paragraph in the left column starts out "NDMA has been consistently mutagenic and clastogenic in human and rodent cells exposed in vitro."

What does that mean?

MR. FOWLER: Objection, leading, speculation, foundation.

A. Damages DNA, damages the genetic material.

Q. And I think we have probably touched on this quite a bit, but I want to make sure for the record it is clear.

Is there significance to the reference to human and rodent cells exposed in vitro?

A. Yes.

Q. Why?

MR. FOWLER: Objection, leading.

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A. Well, you need to show that what you are finding in animal systems, which are experimental systems, also apply to humans. You see the same -- we have been over this -- you see the same metabolism, the same DNA damage, the same interactions in human cells and animal cells, which supports the risk to humans is similar to what it would be to animals, because you have the same mechanism.

Q. This is -- rephrase.

I want to ask you one question that's not found -- rephrase.

I have a little bit of follow-up to that. The animal studies and the mechanistic analysis you have been talking about is obviously important to your evaluation and your evaluation of the weight of evidence, correct?

MR. FOWLER: Objection, leading, foundation.

A. Yes.

Q. Have you seen epidemiologic data that strongly proves that the animal

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data should be disregarded, have you ever seen anything like that that would overwhelm the animal data with negative findings from epidemiologic studies?

MR. FOWLER: Objection, leading.

A. No.

Q. Are you aware of any study that concludes that NDMA and NDEA are not human carcinogens, have you seen that in the peer-reviewed literature where that has been the conclusion that it is not a human carcinogen?

A. No, there is no study like that.

MR. FOWLER: Objection, form, leading.

A. There is not even speculation.

Q. Looking now at the bottom left paragraph on this page 23 of this article, it says "DNA adducts (in particular O6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in

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NDMA carcinogenicity. Observed variations in carcinogenicity among species and strains correlate well with variations in activity of O6-methylguanine DNA-methyl transferase. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA."

Is that significant to you?

MR. FOWLER: Objection, leading.

A. Yes.

MR. FOWLER: Lack of foundation.

Q. Is that consistent or inconsistent with your own opinion?

MR. FOWLER: Objection, lack of foundation, leading.

A. Completely consistent.

Q. Is that what we were talking about this morning?

A. Yes.

Q. Let's go up now to the top of

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the right-hand column. It states "Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumor formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans."

Do you agree or disagree with that conclusion?

MR. FOWLER: Objection, leading, foundation.

A. I 100 percent agree.

Q. And I'm not going to go through this whole study, but this study also -- rephrase.

I'm not going to go through the whole publication, but this publication also discussed human dietary studies as well and took that into account as well, correct?

A. Yes.

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MR. FOWLER: Objection, leading.

Q. In terms of your evaluation of the weight of evidence, is it similar or dissimilar to what the World Health Organization panel did in this peer-reviewed publication in 2002?

MR. FOWLER: Objection, leading, lack of foundation.

A. Very similar.

Q. And this is a peer-reviewed publication published by the World Health Organization in 2002, correct?

A. Yes.

MR. FOWLER: Objection, leading.

MR. SLATER: Thank you, Doctor. Those are all my questions for now.

THE WITNESS: Thank you.

MR. FOWLER: Counsel, we have been going a little while. I would like a five to ten minute comfort bio break. I think everyone would appreciate that.

MR. SLATER: Sure. We will see

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you in ten.

MR. FOWLER: Thank you.

THE VIDEOGRAPHER: The time is 10:55. This ends media two.

(Recess taken.)

THE VIDEOGRAPHER: The time is now 11:07. This begins media three. You may proceed.

EXAMINATION BY MR. FOWLER:

Q. Doctor, I have some follow-up questions related to what you were asked about today. And I just want to note out of the box here that on behalf of the defendants we specifically reserve our time to question you at a later time on all liability opinions per the agreement with counsel. We intend to abide by that agreement, so I'm not going to get into that. So we reserve all rights to question you on that and your qualifications for giving such opinions. I just want to make that clear.

Now, Doctor, the WHO 2002 document that we were last looking at, do

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you recall the statement that counsel showed you that WHO asserted that because there were similarities in the metabolism of NDMA in the animals, that's why they were extrapolating to humans, do you recall that portion of the document you were shown?

A. No, I have to look at it.

Q. Well, let me just, in the interest of time, Doctor, do you recall --

A. Let me just find it.

MR. FOWLER: Then we will need that exhibit put up, if the doctor wants to look at it, let's put that same page up that counsel showed last, please.

MR. SLATER: He wants to have access to the full article also depending on your questions.

MR. FOWLER: Certainly.

THE VIDEOGRAPHER: Counsel, do you know what page that was?

MR. FOWLER: The page number was obscured, so no, I don't.

MR. SLATER: Did you want to

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know the page number, is that what you are asking, Steve?

MR. FOWLER: Yes, just that page you were showing him. I have follow-up on that.

MR. SLATER: It was page 23.

MR. FOWLER: Thank you. If you can zoom in on that so we can see.

THE VIDEOGRAPHER: On which portion, Counsel?

MR. FOWLER: Just the whole document if you can zoom up on. I'm interested that first column in those paragraphs that begin "With the exception." Thank you.

Q. Doctor, it's at the bottom of this column, you see the statement that "The putative pathways for the metabolism of NDMA are similar in rodents and humans," do you see that, Doctor?

A. No, I can't read it. Can you make it larger?

Q. Okay. Now are you with me, Dr. Hecht?

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A. Yes.

Q. Do you recall our discussion yesterday of the Gombar article, sir?

A. Gombar?

Q. He is the pharmacokinetics --

A. That was one of the pharmacokinetics. There are actually several Gombar articles.

Q. That's right.

A. So I don't know -- I don't know which one you are referring to.

Q. Well, the one that I showed you, Doctor, do you recall the statement that the hepatic, and you agreed with this I believe, that hepatic blood flow is dissimilar between humans and the animals studied and that you cannot compare the metabolisms -- let me -- let me strike that and rephrase.

Doctor, the article I showed you yesterday with Gombar if you recall said that the hepatic blood flow comparison between humans and animals is dissimilar, and you agreed with that, correct?

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A. No, I don't remember. You would have to show it to me again.

Q. Is it your testimony, Doctor, that the hepatic blood flow is the same with humans as it is with the rodents that are studied?

A. I don't remember.

MR. SLATER: Counsel, do you think you could put the article up?

MR. FOWLER: I'm just asking his understanding of a comparison right now.

A. I thought you were talking about the Gombar article.

Q. Okay, we will do that. Let's have that, the Gombar exhibit from yesterday.

THE VIDEOGRAPHER: Do you have the exhibit number by any chance?

MR. FOWLER: I don't have the exhibit number. It was the only Gombar article that I introduced.

THE WITNESS: There were several Gombar articles.

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MR. FOWLER: The one that I introduced.

THE VIDEOGRAPHER: I got it. I just had to figure out which one he was talking about. One second.

MR. FOWLER: That's the one.

Q. Now, I will just direct your attention again to the fourth page of the article. It is article page 4369.

MR. SLATER: I can't read it. It is a little small. Can it be blown up?

A. I can't read that.

Q. So at the bottom of the first complete paragraph --

THE VIDEOGRAPHER: Sorry, Counsel, you cut out a little bit. Can you say that again. The bottom of what?

MR. FOWLER: Of the first paragraph that starts at the top, it is just the bottom that I'm looking for.

Q. Doctor, the last sentence, you see "The use of carcinogenicity data obtained in small species (rodents) to estimate risk in larger species (humans),

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which do not take these differences into account, may introduce an error."

Do you see that, Doctor?

A. Yes, I see that.

Q. And the differences being addressed by Dr. Gombar are the differences in metabolism of NDMA between species, correct, sir?

A. So you want to discredit like the national toxicology program. I mean, how, you know, how are we going to evaluate the toxicity and carcinogenicity of substances in the environment and in our food, for example, without animal studies. You want to -- you want to discredit that by just saying that oh, yeah, there is some differences.

Yeah, there are some differences, but NDMA carcinogenicity has been shown in multiple different animal species. So yeah, there are some differences, and Gombar points this out, because probably the reviewers told him to. Sure, there are differences between the

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rats and humans, sure.

Q. Thank you, Doctor. And --

A. I don't see your point. What's your point?

Q. Okay, thanks. The point is while -- you can take that down -- while there may be qualitative similarities between humans and species, you agree quantitatively, Doctor, quantitatively there is -- they are dissimilar with regard to both the ability to metabolize, the amount of DNA repaired capacity, these are different between a rodent that lives two years and a human that lives 30 times that, correct?

MR. SLATER: Objection to form of the question.

A. No, I do not -- I absolutely do not agree.

MR. SLATER: Just let me object. I object, it is compound and overbroad question. You can answer, Doctor.

A. I absolutely don't agree.

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Q. You don't agree that qualitatively the human metabolism of NDMA and the compounds like the MGMT that are involved in DNA repair, you believe qualitatively that is the same in rodents?

A. Qualitatively, they are similar, but, you know, the rodents that were used for these studies are inbred. Humans have a huge variation.

Q. So quantitatively, you --

A. So which -- which human are you talking about?

Q. I'm talking about the plaintiffs in this case, Doctor, and --

A. Which human? Which plaintiff?

Q. Doctor, well --

A. They're not all the same, you know.

Q. Doctor, the simple question is quantitatively, humans and rodents are different in the manner and ability to metabolize NDMA, that's a simple question, do you know?

A. Which human?

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Q. Doctor, the human species, from a qualitative -- strike that -- from a quantitative standpoint, the human beings' capacity to metabolize NDMA and to repair mutations resulting from NDMA are quantitatively different than rodents, do we agree on that, sir?

A. No, we do not agree.

Q. Okay. Doctor, do you --

A. Which human? I go back to, you know, you can't treat all humans the same.

Q. Doctor, if you don't know what the --

A. Not all humans are going to respond to NDMA, as an example, in the same way.

Q. Move to strike. I don't know what that was in response to, Doctor. Let's move on.

A. It was in response to your question. You said, you know, rats -- you want me to say that rats are different from humans quantitatively, and I'm asking you which human.

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Q. And I'm asking you whether you can simply agree that they are different, Doctor. The human species, mammalian species of humans, have a different quantitative ability to fight toxins that have evolved since the time of the caveman grilling their meat and creating NDMA, right, it has evolved; isn't that true, Doctor?

A. Say it again. I didn't really follow.

Q. You agree that the human liver to support a human that is going to live maybe 70, 80 years, has a greater capacity to handle toxins like NDMA than a rodent who is going to live two years, can we agree on that basic question?

A. Which human?

Q. Really, Doctor?

A. One with a liver problem? You know, which human? How about the effects of age? How about the effects of genetics?

Q. Are we a little outside your expertise as an organic chemist, Doctor, to

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start talking about risk factors and things like that?

A. Well, that's what we are talking about in this case, aren't we?

Q. Doctor, the WHO document that you looked at, you understood that as a hazard evaluation, correct, not a risk assessment?

A. Yes.

Q. Do you know the difference?

A. Risk assessment is a quantitative exercise. Hazard evaluation is identifying a hazard, you know, in this case dimethylnitrosamine.

Q. Yes, Doctor. And the WHO, nowhere in that document did it say at what dose does NDMA become carcinogenic in humans, did it?

A. No, I don't think -- I don't think -- well, let me look through it. Let me just look.

MR. SLATER: While you do that, Doctor, can I just ask the court reporter to read the question back to me, please,

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because I lost it. I just want to make sure I hear.

(The record was read.)

A. So they have a section on dose-response analysis on page 23, and they say that "Scaling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate for the measures of exposure response developed on the basis of experimental data in animals, since it is highly probable that the carcinogenicity of NDMA is mediated primarily through the generation of an active metabolite."

That's how they address that. I mean, is that your question?

Q. Doctor --

A. And then they go on to quantitation of exposure response for cancer involved calculation of tumorigenic dose, TD50 --

Q. They make no calculation --

A. -- in rats.

Q. Doctor, let me --

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MR. SLATER: Sorry, you are interrupting his answer, sir. Let him answer, please. Don't interrupt him, please.

A. I'm not sure exactly what your question was.

Q. Okay. Well, then I will move on, Doctor. Then I will move on, okay. Notwithstanding --

A. I mean, they do have a section on sample risk characterization.

Q. It is a large book, I understand. Let me ask you a fresh question, sir.

Notwithstanding all of the questions that counsel asked you about the WHO hazard analysis and notwithstanding all of the information they have about NDMA, they nevertheless classified NDMA and NDEA as a Class 2A carcinogen, correct?

A. Yes.

Q. And they did not conclude that it is a human carcinogen, correct?

A. Let me go back to --

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Q. 2A, Doctor, is a probable, but not established human carcinogen, correct?

A. Yes. Let me go back -- let me go back to 1978.

Q. No, actually, Doctor --

MR. SLATER: You can't interrupt. Everybody needs to stop for a second.

A. WHO, the work as part of WHO, let me read here what they said on page 152 of the monograph number 17 on some N-nitroso compounds. "Although no epidemiological data were available, N-nitrosodimethylamine should be regarded for practical purposes as if it were carcinogenic to humans."

Q. Doctor, Class 2A is a --

A. That's what they said.

Q. Class 2A is a probable human carcinogen, correct?

A. Yes.

Q. And it remains so to this day from 1978, or whatever document you want to pick up, to 2021, it remains only a

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probable human carcinogen, we can agree on that?

A. Only? Only?

Q. Doctor --

A. What do you mean, only? It is a probable human carcinogen. I don't want that in my pill.

MR. FOWLER: Move to strike.

Q. Doctor, with regard to the Pottegard study, you don't know, do you, what the exposure, the relevant exposure period of the affected valsartan tablets is, do you?

A. Let me get the Pottegard study.

Q. Let me rephrase and -- let me rephrase, Doctor.

Do you know what the relevant exposure period is for the affected valsartan tablets?

A. The relevant exposure period, as far as I know -- from the studies you mean?

Q. I mean -- you can set aside Pottegard. I'm not going to ask you

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specifically about that, Doctor.

A. You keep changing on me. By the time I find the thing, you are on to something else. Why are you in such a rush?

Q. Do you understand how long the relevant exposure period is for the affected valsartan products? How long were they on the market in the United States?

MR. SLATER: Objection, lack of foundation. You can answer.

A. So I think the issue began in 2012, that's when they started using the flawed manufacturing process, but I guess these didn't reach the market until later. I'm not exactly sure when it hit the market in the U.S., somewhere between three and nine years ago I guess. I don't know, I'm not sure. I'm sure you know.

Q. So notwithstanding having written a report and been working on this case since 2019, Doctor, your opinions are not based on any understanding of how long those pills were actually available to

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patients in the United States, correct?

MR. SLATER: Objection. You can answer.

A. Sure they are. Sure. They are based on everything that is written in the report there.

Q. So notwithstanding your agreement that dose and duration matter, you haven't considered the duration of time that those pills were available to patients in the U.S., correct?

MR. SLATER: Objection. You can answer.

A. You are telling me what I've considered?

Q. Well, you can correct me if I'm wrong, Doctor.

A. I don't know, what is -- what is your question?

Q. The question is, am I correct that you do not know and therefore have not considered the actual time period that the pills at issue in this case were available, the products at issue were available in the

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U.S.?

MR. SLATER: Objection. You can answer.

A. I don't remember right now the exact date that they became available.

Q. Doctor, this morning you spent some time talking about Exhibit 29, the Herron and Shank article, and then you referred to it a couple of other times after that this morning in response to counsel's question. Do you recall that?

MR. SLATER: Objection, lack of foundation.

A. No. Let me find it. What's the Herron and Shank article?

Q. It was Exhibit 29 introduced today, Doctor. Do you recall referencing that in the discussion today?

A. Can we look at it?

Q. Let's throw it up just to refresh the Doctor. This is the article I'm asking about, Doctor.

A. Oh, yeah, Herron and Shank.

Q. And you expressed that this was

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important to you in forming your opinions, is that what I understood from you today?

A. Yes.

Q. And if you can pick up your report, Doctor, and tell me what page that you referenced this article, please. You can -- you can take it down now. I want to wait for an answer on that.

A. I'm sure I mentioned it.

MR. SLATER: Counsel, I know you are concerned about time. Do you want me to help?

MR. FOWLER: I don't.

MR. SLATER: Okay, that's fine.

A. I don't know, I can't find it right now. But I'm sure --

Q. If you want --

A. If I didn't mention it, it is an oversight because, you know, it is an important study.

Q. And can we agree --

A. I know I mentioned -- I don't know. I don't see it right now.

Q. Sure. And if you look to the

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end of your report, you will see you have got your references from all those footnotes, right, sir?

A. Yes.

Q. Why don't you look there and tell me if this article appears in any of your footnotes. Maybe that will help.

A. All right, let me look through it.

(Witness perusing document.)

A. Yeah, I don't see it. You know, that's an oversight.

Q. Okay.

A. It should have been -- it should have been quoted. It is an important study.

Q. Right. Let's move on.

You were asked today about Exhibit 28, the Wang/Hecht article by the esteemed Dr. Hecht. Do you recall that discussion today? And that's in your reference list, yes, sir?

A. Yeah, I'm familiar with it.

Q. Yes, sir. And my question is

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that study dealt with a discussion of the formaldehyde adducts, correct?

A. Yes.

Q. And we're in agreement that formaldehyde is also formed endogenously?

A. Yes.

Q. And you also stand by your testimony yesterday that there is no study with regard to the formaldehyde byproduct, if you will, of NDMA that has established a causation -- let me start that terrible question again.

Doctor, you stand by your testimony yesterday that there is no study that finds that the formaldehyde adduct from NDMA caused any cancer, correct?

A. I don't think I really said it that way, but that's -- the role of formaldehyde as a byproduct of nitrosamine metabolism, it is actually the main product other than obviously the DNA methylating agent, has not been thoroughly evaluated, investigated. That's what I was trying to say.

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Q. I see. Can we agree that every article that you've cited, and you can't point to any others, referred to the carcinogenicity mechanism of NDMA is the formation of the O6-methylguanine mutation; isn't that true, Doctor?

A. That is an established mechanism, yes. That doesn't mean it's -- that doesn't mean it's the only mechanism.

Q. It is the only established mechanism, though, can we agree on that?

A. Yes.

Q. And can we agree that the level of oxidative stress that it would take to cause a malignant transformation is magnitudes higher than you would expect to see from the formation of a formaldehyde molecule from NDMA?

A. What do you mean, oxidative stress? What do you mean?

Q. Are you -- are you familiar with the concept of oxidative stress being related to malignant transformation of cells?

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A. Yes, I'm familiar with it.

Q. And do you know at what level -- what level it would take to achieve that?

A. I need a -- I need a better explanation of what you mean by oxidative stress.

Q. Let me -- I'll withdraw that and move on, Doctor.

None of your discussion in the Wang article with regard to the formaldehyde adducts suggests that that is a cause of carcinogenicity when the animals you studied were exposed to NDMA, correct?

A. I don't know about none. I mean, I don't know about none. I mean, formaldehyde can be carcinogenic and, you know, so this is -- this is a plausible additional contributing mechanism to NDMA's carcinogenic effect. So I don't -- I don't know that you can say none.

Q. Doctor, I'm asking about your study. You actually have personal knowledge of this, right?

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A. Yes, I do.

Q. And nowhere in the study data that you have published did you conclude that the formaldehyde adducts resulted in carcinogenicity in any of those animals; isn't that accurate? I mean, maybe I missed it in the study.

A. No, we -- we couldn't conclude that. That wasn't really the purpose of the study.

Q. You weren't concerned about it?

A. You know, DNA cross-links are considered genotoxic, and we identified cross-links in the study, so that, you know, this was a possible contributing mechanism that hasn't been evaluated before.

Q. Or since, correct, Doctor?

A. Correct, for dimethylnitrosamine.

Q. Doctor, you testified earlier this morning that human metabolism is important, is essential to transforming NDMA into a mutagenic substance, correct,

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Doctor?

A. Yes.

Q. And you would agree that that specific cytochrome P450 E1 enzyme must be present in a tissue with NDMA in order to metabolize it, right?

A. No.

Q. It doesn't need that cytochrome P450 E1 enzyme?

A. 2E1.

Q. 2E1, sorry.

A. 2E1 is the most efficient P450 enzyme to metabolize dimethylnitrosamine, but other P450 enzymes also metabolize dimethylnitrosamine, just not as effectively, for example, 2A6. So it's not the only -- it's not the only enzyme that metabolizes DMN, it is just the one that does it most efficiently.

Q. Doctor, do any of the studies that you have cited refer to any enzyme other than the CY452 E1, do any of them refer to that, any of the studies you have cited, refer to any other enzyme?

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A. No. The studies I cited focus on 2E1 because that's the accepted, most effective of the 27 different P450s to metabolize DMN. 2E1 has an affinity for a smaller molecules, but other enzymes, other P450 enzymes, can metabolize dimethylnitrosamine, absolutely, but not as effectively as 2E1.

Q. And you can point to nothing, no scientific article that says that, can you, Doctor?

A. I can, yeah. I can definitely point to scientific articles that will say that, absolutely. Here, read the book by Ortiz de Montellano on P450. You will find it in there, okay? Just read it.

Q. Thank you.

MR. SLATER: One second, Doctor. That is a book called Cytochrome P450?

THE WITNESS: Cytochrome P450: Structure, Mechanism and Biochemistry.

Q. Can you please --

THE WITNESS: Fourth Edition.

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Q. Can you please open up the book to where you have that bookmark and tell me what page that's on, sir?

A. The bookmark has nothing to do with this case.

Q. Nevertheless, Doctor, just tell me the page, please.

A. 540.

Q. Thank you.

Doctor, do you know who Dr. Andrew Teasdale is? Have you heard of him?

A. Who?

Q. Dr. Andrew Teasdale.

A. Spell it.

Q. T-e-a-s-d-a-l-e, an analytical chemist. Are you familiar with him or his writing?

A. Not offhand, no.

Q. And if he is published in that book you are holding, you would -- well, strike that.

Do you find that book to be an authoritative book on the CY450 enzyme,

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Doctor?

A. Yes.

Q. You would rely on that in your regular practice outside of litigation?

A. Yes.

Q. And did you in fact use that as a resource at all in forming your opinions in this case?

A. I didn't quote it, if that's what you mean. Sure, it is a resource, because it is in my brain.

Q. Yes, sir. And can we just agree at a high level, sir, that a metabolic enzyme needs to be present in the tissue with NDMA in order to metabolize it?

A. Yes.

Q. Okay. And absent --

A. Metabolism is required for the carcinogenicity of NDMA, definitely.

Q. And can we also agree, Doctor, that not every tissue or organ system in the human body produces a metabolite that is capable of metabolizing NDMA?

A. I don't -- I don't know if we

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have that data. Every -- every organ system in the human body, I don't think we have that data.

Q. Doctor, do you recall earlier looking at --

A. I mean, you know, in science we depend on data.

Q. Thank you.

Doctor, do you recall earlier looking at the article that was about colorectal cancer, it was that large cohort study, sir?

A. Yes.

Q. And you recall that in that abstract that we looked at, it stated there was no association found with the stomach cancer, do you recall that?

A. Yes.

Q. And you agreed -- you agreed with that, that there was no evidence, I think was your testimony, there is no evidence that the NDMA causes stomach cancer, correct, that was your testimony?

A. In laboratory animals, correct.

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Q. Okay. So then you wouldn't be sure if it does in humans, is that what you are saying?

A. Well, that study did not show an effect in stomach cancer. I think -- I believe what I said was that that's consistent with all of the animal studies, which as far as I know have never shown stomach cancer.

Q. And, Doctor, do you agree that in order for there to be colorectal cancer caused -- allegedly caused by NDMA, the NDMA would have to get to the colorectal space, correct?

A. No. It is possible that a metabolite NDMA could be transported to the colon. We don't know. So even though the alphahydroxy metabolite NDMA that we have been talking about for the last couple of days, even though that's unstable, it is still possible that some of it may get conjugated to form an alpha-acetoxy-dimethylnitrosamine which would be stable and could be transported to

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other tissues.

That hypothesis has been out there, not thoroughly tested, but it's possible that the alphahydroxy metabolite could actually get conjugated and then the conjugate could be transported to another tissue and then deconjugated. That's how you could get -- that's one way you could induce tumors in the colon.

Q. And you are hypothesizing, correct, Doctor?

MR. SLATER: Objection.

A. I'm hypothesizing, but this is not something I just thought of. I mean, this is -- this pathway has been speculated before in the literature.

Q. As you said a minute ago, the hypothesis has been out there for a while, right?

A. Yes.

Q. And to date no study has been done that demonstrates in an animal or a human that there is that conjugation of this highly reactive metabolite?

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A. As far as I know, that's correct.

Q. Okay.

A. That doesn't mean it doesn't happen.

Q. Thank you.

Now, Doctor, moving on to the discussion counsel had with you this morning with regard to the FDA panel, Doctor, do you agree that the FDA convened that workshop because FDA is uncertain that the acceptable intake of 96 nanograms is appropriate, that's why they convened a workshop; is that a fair statement?

A. I don't know why they convened a workshop.

Q. Well, you do know that they --

A. I think they became aware of this horrible problem and they didn't really know what to do about it and they didn't really -- I think they were probably a little bit blindsided, and all of a sudden they found out, my God, you know, there is dimethylnitrosamine in valsartan,

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what are we going to do?

And so, you know, they probably had some focus groups and discussions and they decided well, why don't we get some experts together on nitrosamine carcinogenesis and see what they say, maybe they can -- maybe some good advice will come out of this. That's why I think they convened the workshop.

Q. So do you know approximately -- strike that.

FDA declared the 96 nanogram acceptable intake somewhere in the 2019 time frame, correct?

A. I don't know. I have that here. Let me see. Let me see here. The 96 nanograms per day, the recommendation was published September 1st, 2020.

Q. Okay.

A. That's not -- that's not in the 2019 time frame.

Q. Thank you for the clarification.

A. September of 2020 is not in the

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2019 time frame.

Q. Thank you. I would like to mark what you are holding as Exhibit 31. Please make a copy and send it.

A. That is from C&E News published September 7th, 2020.

Q. Thank you. We are going to mark that, Doctor.

(Hecht Exhibit 31 deemed marked for identification.)

Q. Behind you, you have got manila folders, Doctor. What are in those folders?

A. Those are some manuscripts I'm working on.

Q. Anything to do with this case?

A. Why do you ask?

Q. Well, because I'm entitled to know what you have with you at the deposition, sir. That's all.

A. I see.

MR. SLATER: The question is whether it relates to this case.

A. I'm sitting in my office, and,

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you know, the stuff on my desk are things I'm working on.

Q. Yes, sir, no problem.

Doctor, so they came up with that in September 2020, and in March 2021, Doctor, one of the questions the FDA panel posed was question 4, whether or not the exogenous and endogenous levels should be considered with their acceptable intake assessment, correct?

A. Sure.

Q. And, Doctor, you --

A. We have been through this.

Q. Yes, sir. And you agree, Doctor, that -- let me start that again.

Doctor, have you ever testified that NDMA is in fact produced endogenously?

A. I don't believe so. Testified?

Q. Yes, sir.

A. No.

Q. Bear with me.

Do you recall the -- do you recall the case of Tuttle versus Lorillard? This is one of your tobacco litigation

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cases, Doctor.

A. Yeah, that was like more than ten years ago.

Q. Okay.

A. When was it? Refresh my memory.

Q. Yeah, on August 29th, 2002. Let's put the transcript up.

A. 2002?

THE VIDEOGRAPHER: Counsel, just give me one moment. I'm looking through your documents to try and find it.

What is the case name again? I'm sorry.

MR. FOWLER: It is T-u-t-t-l-e versus L-o-r-i-l-l-a-r-d. We labeled them with a date, 8-29-02, that's how we I think submitted it.

THE VIDEOGRAPHER: Gotcha. I think you guys must have added that yesterday. I didn't have it in my documents.

MR. FOWLER: Yes, sir. No, we added it this morning probably.

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THE VIDEOGRAPHER: This morning, that's what I meant. Just give me one extra second here.

Would you like to mark this as the next exhibit?

MR. FOWLER: Yes, please.

THE VIDEOGRAPHER: So that will be 32.

(Hecht Exhibit 32 marked for identification.)

MR. FOWLER: The article that the doctor held was 32 and this will be 33?

THE VIDEOGRAPHER: The article the doctor has is 31.

MR. FOWLER: Thank you. Then this is 32.

Q. Doctor, do you see this is a transcript from United States District Court, District of Minnesota, that's in your backyard, correct, sir?

A. Yes.

Q. Seeing this caption, does this refresh your recollection of being involved in this case?

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A. Yes, it does.

Q. Directing your attention to page 208.

THE VIDEOGRAPHER: One moment, let me find that page.

Q. Doctor, line 8, "Question: Among the indigenously formed nitrosamines you would agree NDMA is one of them?"

Your answer: "NDMA, the evidence of indigenous, yes, there is evidence for indigenous formation of NDMA. I would agree."

Do you see that, Doctor?

MR. SLATER: Do you want to read the rest of the answer?

A. Yeah, "But it is not one of the ones where the evidence is so very strong. But yes, there is evidence for indigenous formation of NDMA".

So, I mean, this is exactly what I was saying yesterday, okay? I mean, you can find it in the literature, and at that time, you know, this was 19 years ago, but those methods have been totally

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discredited.

Q. Doctor --

A. This was -- this was -- this was a true statement in 2002, but it is not correct.

Q. There has been evidence since that time that discredits this statement, Doctor, is that what your testimony is right now?

A. Yes.

Q. And what evidence is it that discredits what you believed under oath in 2002?

A. You know, the methods that they used in those studies were not valid. There is cross-reactivity. There is other problems. I don't -- I don't remember all the details right now, but the methods aren't valid.

Q. Doctor, you would agree that the technology, if anything, has improved since 2002, correct?

MR. SLATER: Objection. You can answer.

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A. What technology?

Q. The technology to detect things like NDMA, for example.

MR. SLATER: Objection. You can answer.

Q. In the body.

A. Yes.

Q. And the ability to isolate the adducts caused by NDMA, that technology has dramatically improved since 2002, correct?

A. Absolutely.

Q. And, Doctor, it is not your opinion that NDMA is not endogenously formed, is it?

A. Double negative.

Q. Yes, I know.

A. I'm saying we don't have the data, okay? Why is that complicated? I have said this over and over. I think I said it 100 times in the last two days. We don't have the data, okay? Why is that complicated? Why do you guys keep harping on that?

Q. Doctor --

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MR. SLATER: Take it easy. We are almost done.

A. There is no good data out there.

MR. FOWLER: Can you take that down.

A. So why don't you just believe me?

Q. Doctor, the data that you are referring to has to do with the measurement of the level of endogenously produced NDMA, not whether or not it is endogenously produced, correct?

A. I don't see the difference. If it's not endogenously produced, then there is -- there wouldn't be a level above and beyond the exogenous exposure.

Q. Maybe my question wasn't phrased right.

The scientific question, Doctor, is not whether or not NDMA is endogenously produced, it is how much, correct?

A. No, it is both. It is whether

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it is endogenously produced, and if it is endogenously produced, how much. It is both. It is relevant.

Q. And are you --

A. If there is a lot of endogenous production, then that obviously has an impact on the exogenous exposure. So, you know, the extent to which it is endogenously produced is highly relevant.

MR. FOWLER: Let's put up that Exhibit 13, please. I just want to follow up on a question that was asked this morning, page 16. Thank you.

Q. Doctor, question 5 is "Should the regulatory" -- you don't have to blow it up, we can read it --

MR. SLATER: I can't.

MR. FOWLER: Okay, thank you, then blow it up from there to the bottom of the page.

MR. SLATER: Thanks. My eyes are starting to --

Q. The question FDA posed to the workshop, Doctor, "Should the regulatory

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limits for nitrosamines listed for food and water, or amount formed endogenously, be considered in determining AI of nitrosamines?"

That was one of the questions FDA posed to this panel of the variety of experts before it, correct?

A. Yes, yes.

Q. And if we look to the last paragraph, the "Also, determination," do you see that?

A. Yeah, I see it.

Q. The next sentence states "The argument for a no answer was that if exposure from all sources other than drug contamination is large, then the health risk from the small amount present in drugs becomes insignificant."

Do you agree with that conclusion from this FDA panel, Doctor?

MR. SLATER: Objection.

A. I don't know why we keep going over this, okay? I think I've stated my opinion multiple times already. The issue

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is we don't have the data, okay? If in fact there is an amount of endogenous dimethylnitrosamine formation that's far larger than the exogenous exposure from these contaminated pills, then the exogenous exposure would not be such a concern.

Q. Thank you, Doctor. I will move on.

A. But we don't have the data, as I have said repeatedly, and I don't know why you guys keep trying to twist what I said in the FDA meeting. That's what I was saying in the FDA meeting, but you guys want to take every word and somehow twist it around to have a different meaning.

Q. Doctor --

A. So, I mean, I'm a little tired of that.

Q. Doctor, respectfully --

MR. SLATER: Dr. Hecht, don't worry, we are almost done.

Q. Doctor, respectfully, you disagree with the data, it is not that

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there is no data, correct?

MR. SLATER: Objection. Counsel, let's not argue anymore. If you have a question --

A. The data is --

MR. SLATER: Dr. Hecht, Dr. Hecht, there is no question. All he did was make a statement at you. Counsel is not going to be argumentative. He didn't ask a question. There is nothing to respond to. Let's take it down a lot of notches. We are almost done. Let's just slow down. We are almost there.

MR. FOWLER: Thank you, Counsel. You can take that exhibit down.

Q. Doctor, isn't your position that you disagree with the data that was presented at FDA's workshop by another one of your fellow experts on the level of endogenous formation, you disagree with that data?

A. Yes, that's true.

Q. It's not that there is no data, you disagree with it?

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A. That's true.

Q. Okay, thank you.

Now, let's move on. You were shown today the FDA Guidance for Industry.

MR. FOWLER: Can we have that exhibit up. This was something new.

THE VIDEOGRAPHER: Are you aware of the exhibit number by any chance?

MR. FOWLER: No, I don't. It was the third one introduced today, so I'm going to go with 27.

THE VIDEOGRAPHER: 27 was the first document introduced today, or second, but the first new one. Let me see, I will pull up 27 and you let me know if this is right.

MR. FOWLER: It is the FDA guidance. I just didn't note the exhibit number. Oh, well done, okay. I hit that one.

Q. Doctor, first of all, do you recall the questions counsel asked you with regard to FDA's methodology, if you will, that they applied in reaching their

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acceptable intake?

A. Was this yesterday?

Q. No, this morning, this is what you and counsel talked about.

A. Yeah, I guess.

Q. Let me direct your attention to page 10 of this document. And you've seen this document before today, is that a fair statement, Doctor?

A. Uh-huh.

Q. And, Doctor, do you -- are you familiar with the ICH M7(R1) regulatory document as well?

A. Not offhand. I'm not sure what that is offhand.

Q. Fair enough.

A. What is ICH?

Q. If we can blow up that paragraph second from the bottom, "If nitrosamines."

"If nitrosamines without published AI limits are found in drug products, manufacturers should use the approach outlined in ICH M7 (R1) to

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determine the risk associated with the nitrosamine and contact the Agency about the acceptability of any proposed limit."

Doctor -- you can take that down -- Doctor, are you familiar with the alternative method of calculating the risk that is accepted by FDA in ICH M7 called the BLDM approach?

A. Am I familiar with it? I have heard of it. I know what it is, okay? The benchmark lowest dose, but I don't -- I don't -- this is not -- it's not what I do.

Q. Okay. Well, I will just have --

A. But I'm familiar with it, like, you know, you're familiar with the mechanism of hydroxylation.

Q. Oh, thank you.

A. You're welcome.

Q. Let's look at the ICH M7 very quickly. I have a very simple question for you on this. I will direct your attention to note 4 once it's up.

THE VIDEOGRAPHER: This is a

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new document, correct, Counsel?
MR. FOWLER: Yes, it is the ICH M7 2017 edition.
THE VIDEOGRAPHER: This will be Exhibit 33.
(Hecht Exhibit 33 marked for identification.)
Q. If we can go to Section 7.2.2, I think it is on page 8 perhaps. Okay, if we can highlight that.
Doctor, do you agree that there is sufficient carcinogenic data with NDMA that has established the existence of mechanism with regard to the dose-response?
A. Yes, there is good dose-response data.
Q. And do you have an opinion whether there is sufficient dose-response data to use the alternative approach to the AI and use that data to calculate the PDE, do you believe there is sufficient data for that or do you not have an opinion?
MR. SLATER: Objection. You can answer.

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A. I don't have an opinion right now. I mean --
Q. Okay.
A. You are throwing this stuff at me. I would have to think about it.
Q. Okay. You can take that down.
Doctor, the Johnson -- the Dr. George Johnson study that counsel reintroduced today, I'm correct that you didn't read or rely on that in forming your opinions, right?
A. Correct.
Q. And do you agree -- let's put that exhibit up, please. I can't remember the number, but it was up today.
THE VIDEOGRAPHER: Counsel, what was the document?
MR. FOWLER: The George Johnson permitted daily exposure limits.
MR. SLATER: Hey, while you are looking for that, I just want to make sure, would the court reporter, please, Todd, that we have the appearances of everybody who is attending this deposition, including

S. HECHT
anybody who is watching it or watching the realtime. I assume, counsel for the defense and everybody else has disclosed themselves for the record as to everybody that is participating. I just want to make sure that we have that.
Has everybody been giving their appearances? And if anyone else is watching, like a defense expert or anyone else, that should be documented in the transcript. I'm making sure we have all that.
THE COURT REPORTER: I've looked at the participant list and tried to jot everyone down.
MR. SLATER: All right, I just want to state for the record that we certainly obviously expect that everybody enters their appearance, and that includes anybody that is watching this deposition, like if counsel has an expert sitting in their office, I assume they will be disclosed.
MS. LOCKARD: I can represent

S. HECHT
-- this is Victoria Lockard for the record -- we do not not have any experts sitting in on this deposition. Daniel Nigh at the Madigan deposition made it clear that plaintiffs take the position that would be inappropriate, so I want to make sure that plaintiffs agree and will not have experts in their taking of our depositions, and we could take it up off the record, but to answer your question, we don't have an expert sitting in, and if plaintiffs intend to do that we need to have a discussion off the record about it.
MR. BALL: Hey, Adam, I can state for Duane Morris that we do not have any experts.
MR. SLATER: No problem. I wasn't accusing anybody. I just wanted to make sure that we had, you know, but we can talk about it another time. Obviously I can't speak for everybody right now. I hadn't even thought about the issue. It just crossed my mind.
MR. FOWLER: Dr. Johnson is off

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camping, I'm not in touch with him.

Q. Looking at this exhibit --

THE VIDEOGRAPHER: Mr. Fowler, you went on a tangent before I could get the answer, was it an exhibit that was marked today or was it a previously marked exhibit?

MR. FOWLER: It was previously marked. Let me get you that number, 16 I believe, I may be off by one, but I think it was 16.

THE VIDEOGRAPHER: The document title was the --

MR. FOWLER: Was Permissible Daily Exposure Limits.

THE VIDEOGRAPHER: So it is not 16, it might be 17.

MR. FOWLER: Yeah, I think I'm off by one somehow.

THE VIDEOGRAPHER: I don't think it is 17.

MR. FOWLER: It could be 15. There is a note, 15 is missing from the exhibit site, but I have Johnson as 16. I

S. HECHT

don't know. It was just up this morning. Super, thank you so much.

Q. Doctor, do you have an opinion whether or not -- let me start that again.

After we mentioned this article yesterday, Dr. Hecht, did you read this during the break?

A. No.

Q. Overnight or whatever? No?

A. No.

Q. This article was referenced at the FDA workshop panel as well. Do you recall that?

A. No.

Q. Do you have any understanding -- let me start that again.

Dr. Johnson, according to this article, established a point of departure, a POD, are you familiar with that terminology?

A. I have heard of it, yeah.

Q. Are you in a position, do you feel qualified to agree or disagree with Dr. Johnson's point of departure for his

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NDMA analysis in this study?

A. Not really. I think I've said repeatedly that this is not what I do.

Q. Okay. Let's look at the introduction. I just --

A. I don't do -- I don't do risk assessment. I don't do risk calculations.

Q. Yes, sir. Well, that helps.

In the paragraph, just scroll down a bit, we are going to use that starting "With nitrosamines" paragraph, but I need further down. You see about halfway down, it starts "MGMT's ability," Doctor, do you see where I am?

A. No.

Q. Scroll a little bit down. There you go. "MGMT's ability to remove base alkylations and restore the normal wild-type DNA sequence represents an error-free damage response that can mechanistically account for the manifestation of a dose-response threshold."

First, Doctor, do you

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understand that sentence?

A. I'm not sure.

MR. SLATER: Take your time, Doctor.

A. I'm not sure exactly what he is trying to say here.

Q. Okay. Okay, that's fine.

A. Sure, I mean, MGMT does restore the damaged DNA to its original form.

Q. Okay.

A. It is an error-free DNA damage response. Whether that can mechanistically account for the manifestation of a dose-response threshold, I'm not sure about that.

Q. That's fine. You can take that down.

A. I think it is an oversimplification.

Q. Fair enough. You can take that down.

MR. SLATER: What page was that again, was that 296?

MR. FOWLER: Oh, gosh, I think

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so.

THE VIDEOGRAPHER: 294 was the page.

MR. SLATER: Thank you very much.

THE VIDEOGRAPHER: Counsel, for the record, just so you know, that was Exhibit 14 to the deposition.

MR. FOWLER: Oh, super, thank you.

Q. Now, Doctor, earlier today you were asked questions about your report, pages 24 to 26, about the levels of NDMA measured in finished dose products and the API. Do you recall those questions?

A. Yes.

Q. And in your report you cite to witness testimony from different manufacturers, correct?

A. Right, yeah.

Q. Is that the sole basis for your statements in your report was the defendants' witness statements, in those paragraphs on page 24 to 26, where you are

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talking about the levels?

A. Yes.

MR. SLATER: I'm sorry, what was the question? Wait one second, Doctor. What was the question? It got missed. Can you just clarify the question?

MR. FOWLER: Sure.

Q. My question is simply is the sole basis for the statements in the paragraphs about each of the manufacturers the statements made by the defendants' witnesses that you cite to there?

A. This is based on the information that was available to me.

Q. Okay. And am I correct you didn't endeavor to evaluate independently any of the statements made by those witnesses? And by that you didn't evaluate independently any of the company documents that may or may not have confirmed those statements?

MR. SLATER: Objection, lack of foundation.

A. No, I looked at the company's

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documents. I mean, I looked at very extensive lists of different batches of valsartan API and their levels of contamination. I looked at that.

Q. Okay. Well, for example --

A. I saw that, so I know what the part per million levels of NDMA were in literally hundreds of batches, I've looked at that data.

Q. And, Doctor, do I recall correctly your testimony yesterday, and this is kind of in your wheelhouse as an organic chemist, that the levels of NDMA in the API, the active pharmaceutical ingredient, would not be the same as in the finished dose, I think we established that would be lower in the finished dose, yes?

A. That depends how much inactive material is added to the API to make the finished dose. That's what it depends on.

Q. Right. But you would expect, Doctor, that the finished dose levels would be lower than the API levels, correct?

MR. SLATER: Objection.

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A. I don't know how much excipient was added.

Q. Okay, fair enough. And you made no effort to try to determine the proportion, if you will, of API to finished dose, you made no effort to extrapolate the levels from API to finished dose levels, did you, sir?

A. No, I didn't.

Q. And you took at face value, if you will, any witness statement that may have incorrectly alluded to the API levels and the finished dose levels being the same?

MR. SLATER: Objection.

A. I don't know if --

Q. That was a bad question. Let me withdraw that.

MR. SLATER: Counsel, are you saying that your 30(b)(6) witness on behalf of your client, Teva, didn't tell the truth and wasn't accurate when he spoke for the company in his deposition?

MR. FOWLER: I said nothing

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like that, and I withdrew the question because I was afraid somebody might misunderstand it.

MR. SLATER: Sorry, I was that guy.

MR. FOWLER: Maybe.

Q. Bear with me, Doctor. I just want to check a couple of notes.

Doctor, after last night did you review any of your materials or do any additional research during the break, during the overnight, sir?

A. No, I went home and watched the Twins game.

Q. How did they do?

A. Had a glass of wine. They lost.

Q. It wasn't the end of the day you were hoping for then, right?

A. We're used to it.

Q. Did you -- did you discuss your testimony with Mr. Slater or any other counsel between last night's session and today, sir?

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MR. SLATER: Objection. Don't answer that question. That's not --

MR. FOWLER: I'm not asking what, I'm asking if.

MR. SLATER: Doctor, wait. It is not a reasonable question. You are not allowed to ask what happens in between breaks, and I assume everybody agrees. Do you want us asking your experts what you talked to them about during the breaks or overnight?

MR. FOWLER: Counsel, I didn't ask anything like that.

MR. SLATER: You did.

MR. FOWLER: I asked if there was a conversation. That's where I stopped the question.

MR. SLATER: Oh, without subject matter, you are just saying did we communicate?

MR. FOWLER: Yes, sir, that's all I asked.

MR. SLATER: Okay. That question you can answer, Doctor, with a yes

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or no.

A. Yes.

Q. And do you recall for how long?

A. No.

Q. Doctor, do you feel -- oh, I know what I was going to ask you. Doctor, anywhere in your report do you refer to the RAS oncogene? Do you refer to that anywhere in your report?

A. I believe so.

Q. Can you point to any study, any statement in your report where you are attempting to express an opinion of the RAS with regard to the RAS oncogene mutation and NDMA? You mentioned it again today, so that's why I'm following up.

A. Well, I mention O6-methylguanine in DNA causes G to A mutations. I don't think I actually mentioned RAS here.

Q. Did you research or review -- wait, I'm sorry.

MR. SLATER: Counsel, he is still talking.

S. HECHT

MR. FOWLER: I'm sorry.

MR. SLATER: He is still talking. Do you want to finish, Dr. Hecht?

THE WITNESS: I'm finished.

Q. Doctor, did you do any research specifically with regard to the RAS oncogene in forming your opinions in this case?

A. Did I carry out research or did I review the research? I don't understand your question.

Q. Let me try again.

Can you point to any materials in your materials reviewed list that you relied upon for any opinions with regard to the RAS oncogene specifically and any NDMA mutation, sir?

A. Sure. I mean, we talk about it in reference 43. We talk about it in reference 37. We talk about it in reference 19. They talk about it in reference 25.

Q. Doctor, are those references that you are listing off --

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A. They talk about it in reference 10. You know, all of these references talk about RAS, about mutations in RAS.

Q. Okay. That's what I was trying to make sure you were answering.

Even though those references in your report where you had those footnotes, you don't speak of RAS, it's your opinion that those articles you have just listed off are what you were relying on for any opinion on RAS oncogene mutation?

MR. SLATER: Objection. You can answer.

A. They are referenced in those other articles -- it is referenced in those other articles.

Q. And you agree, of course, Doctor, that RAS oncogenes are also subject to DNA repair?

A. Yes.

Q. And do you know -- and in order for a RAS oncogene to be affected by NDMA, you would agree it would have to be the AG mutation, right?

S. HECHT

MR. SLATER: Objection. You can answer.

Q. The guanine --

A. It is G to A.

Q. G to A mutation right?

A. That's what's normally seen with dimethylnitrosamine, G to A.

Q. And if it is a G to T mutation that is seen on a RAS oncogene, you would agree that's not caused by NDMA, right?

A. That's what the evidence indicates, yes.

Q. And if there is an A to T mutation, that would also not be caused by the NDMA, correct?

A. I'm not sure about that.

Q. Okay.

A. I mean, I have to say, again, there might be other pathways involved in NDMA mechanisms. You know, everybody talks about O6 methyl G and RAS and G to A because, I mean, there is great evidence for that, and, you know, it all flows, it all fits together, but there are multiple

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possible -- there are multiple -- not possible; known -- DNA damaging pathways of NDMA, okay? 06-methyl G is not the only -- it's not the only adduct that is formed. You have 7-methyl G is a major one. You have adducts on phosphate. You have adducts on thymine. You have adducts on adenine. You have adducts on cytidine.

So you have a whole -- a collection of DNA adducts. The focus has been on O6-methyl G, and G to A, and RAS, because we know that that is the sequence. So that's what everybody focuses on. But that doesn't mean there aren't other mutations also that might be important.

Q. And that's a hypothesis, right, Doctor?

A. I think it is more than a hypothesis. We know that NDMA doesn't only form O6-methylguanine, this is established, NDMA hits every base in DNA and it hits every nucleophilic site in guanine, so we know this. This is -- this is established science, and the consequences of those

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other adducts have not been fully investigated, so it could be that there are other mutations caused by NDMA that, you know, we're not discussing because we don't have -- we don't have as much data.

Q. And it would be --

A. So you need to keep that in mind.

Q. Yes, sir.

A. You know, it's not -- it's not so simple, okay? So, for example, the 7-methylguanine adduct, which is a major one, causes a depurination leading to apurinic sites, and the apurinic sites themselves in DNA have an effect, miscoding effect.

Q. Thank you, Doctor. And fair to say that you can --

MR. SLATER: Counsel, I'm sorry, I think we are at ten hours.

Q. Thank you for that response, Doctor, and your time and patience in your deposition.

A. You're welcome.

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Q. Do you feel you have had a chance to express all your opinions today and yesterday, sir?

A. Yes.

MR. SLATER: Objection. And I have a few follow-up questions, so I'm going to actually jump in and finish up now. It will take about five minutes, maybe, okay? Thank you.

EXAMINATION BY MR. SLATER:

Q. Doctor, if you could, let's knock a couple of things off real quick. Can you look at your report, please, page 22. Thank you.

You were asked some questions by counsel about whether you had any information about the time periods at issue when the contaminated valsartan was on the market, and I'm just going to point to you a couple of things.

The top paragraph on page 22, the first full paragraph, do you see about four or five lines down it shows that you had reviewed a chart of results of 783

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batches being tested that were manufactured between 2011 and 2018 with NDMA levels as high as 188.1 parts per million from ZHP?

MR. FOWLER: Objection, leading.

A. I reviewed that data.

Q. And you mentioned earlier I think, that in the interest of time I will try to move through this, new question, you mentioned earlier it was your understanding that it took some time from the time the process was completed until the time the pills started to be sold, you understood that from the things you have read, right?

A. Yes.

MR. FOWLER: Objection, leading.

Q. I will give you another example.

If you go to page 25, if you could, there is a discussion at the bottom of the page in Section 6 about the nitrosamines in the Teva finished dose formulation, and at the end of the first

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paragraph it says that "The valsartan finished dose labeled as Actavis and sold in the United States initially was manufactured using ZHP TEA process with sodium nitrite quenching valsartan API, and then ZHP zinc chloride valsartan API beginning in late 2014."

So that was information you had as well?

MR. FOWLER: Objection, leading, foundation.

A. Yes.

Q. And it was your understanding, I'm not going to get into more detail, but you had an understanding that these pills had been on the market for at least several years in varying lengths of time --

A. There is something wrong with your sound, Adam.

MR. FOWLER: I liked it so much better.

(Technical interruption.)

Q. Was it your understanding that the contaminated valsartan was sold in the

S. HECHT

United States for several years, I've shown you a few of the dates, and it varies depending on the manufacturer?

MR. FOWLER: Objection, leading, foundation, facts not in evidence.

A. Yes.

Q. Looking at your report, let's put another thing to bed. If you could look towards the end at Exhibit 3, the list of literature references.

MR. FOWLER: Objection to the colloquy.

Q. Do you see at the bottom of that page, literature reference 13?

A. Yes.

Q. Is that the Herron and Shank article that counsel asked you to locate in your report in your reference list?

A. No, I think I misheard you. Which reference did you say it was?

Q. Are you on the page that says Exhibit 3, Literature References?

A. No, I don't have the --

Q. Oh, it's not -- all right,

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well, take my word for it. I'm going to do something, take my word for it.

A. Okay.

Q. On Exhibit 3 to your report, the list of literature references, number 13 says Herron and Shank, and has the title of the article that we went through.

A. Yeah, right, right.

Q. Is that consistent with your recollection that it was something that you reviewed and that we listed here as something you referenced?

MR. FOWLER: Objection, leading, foundation.

A. Yes, I mean, I have said this, you know, it is an important study.

Q. Okay.

MR. SLATER: Chris, why don't you put up the Gombar study and let's look at the first page, and I think we highlighted one section. There is another one that you -- I think -- let me see the other one. Hang on. It just went away, all right. Can you put that back up,

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please, Chris? That's not the document. All right, let's see which article this is first so we can orient. I want to get done here.

Q. This is the Gombar article that we talked about earlier.

A. Yup.

MR. SLATER: Now can you blow up the highlighted part on page 1, please.

Q. Looking at the bottom of the first highlighted paragraph, the author says "The potential for extrapolation to the human was evident when data from a sufficient number of species varying widely in body weight were available."

Do you see that?

A. Yeah.

MR. FOWLER: Objection, leading.

Q. Is that consistent with the testimony you provided earlier about the study?

MR. FOWLER: Objection, leading, mischaracterizes.

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A. Yes.

MR. SLATER: Okay. You can take that down. Chris, can you bring up the Wang article, please, Dr. Hecht's article. Can you go to page 1146, please, the section Discussion on page 1146, bottom left.

Q. And this starts off the discussion, stating "The results of this study provide the first evidence for the presence of formaldehyde DNA adducts in laboratory animals." Then a little further down, you say "The method was applied to rats treated with the carcinogenic nitrosamines NDMA and NNK, and the results demonstrate for the first time that formaldehyde DNA adducts are produced from these carcinogens, in addition to the well-characterized adducts, which result from diazohydroxides formed in nitrosamine metabolism."

A. Yup.

MR. FOWLER: Objection to form, leading. I'm not sure there was a

S. HECHT

question.

MR. SLATER: I didn't get -- I didn't get a chance to ask another question. I asked if Dr. Hecht saw that. He did.

Q. And is that -- is that responsive to the question from counsel earlier about this study?

MR. FOWLER: Objection, form, mischaracterizing my questions.

A. I don't follow you, Adam.

Q. Well, tell us -- let's take a minute and do it. What does this mean, what I just read?

A. It means that formaldehyde DNA adducts are produced in addition to O6-methylguanine and 7-methylguanine that we have been talking about for a couple of days now. Formaldehyde DNA adducts are also produced in rats treated with NDMA.

MR. SLATER: All right, you can take that down. Can you put up the FDA workshop report, please, Chris, and go to page 17.

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Q. Doctor, you were asked, and let's look at the top of the page, the carry-over paragraph, you were asked some questions by counsel again about discussion of endogenous formation, and I just want to read to you starting with the first full sentence on page 17.

"Nevertheless, traditional and M7 cancer risk is based on 1 in 100,000, which is an incremental risk over that of cancer in the general population, i.e., the background incidence is ignored. In principle this is the more accurate and correct approach, i.e., to consider nitrosamine exposure as a result of its presence only in drugs. This is also based on the uncertainty of endogenous formation. If endogenous exposure is overestimated (i.e., it is not greater than 100 micrograms per day), then incremental exposure from drug contamination becomes more significant conceptually. Therefore, exposure from other sources should not be considered in risk assessment or acceptable

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intake calculations for nitrosamines in drugs. It was acknowledged that investigation of endogenous formation is a relatively long-term goal and a practical approach is urgently needed, therefore, flexibility should be exercised."

Is that consistent with your understanding?

A. Yes.

MR. FOWLER: Objection, leading, foundation.

Q. I didn't get the answer.

A. Yes.

Q. Thank you.

MR. SLATER: You can take that down.

Q. Finally, Doctor -- let's take the document down -- you read to counsel from the IARC 1978 monograph which indicated that NDMA should be treated as cancerous to humans for practical purposes. Would practical purposes include determining whether it is safe to have that substance, NDMA, or even NDEA,

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contaminating valsartan pills as occurred here?

MR. FOWLER: Objection, leading.

A. Yes, absolutely. Absolutely, it would.

MR. SLATER: Thank you very much, Doctor. I have no other questions, and since counsel has no more time, we're done.

THE WITNESS: Thank you. It has been nice talking to you.

MR. SLATER: That magazine paper, we will take care of getting, if you could just maybe have a copy sent over to Chris at some point, we will send it over to the defense, that is no problem, that little two-sided piece of paper from the magazine.

THE WITNESS: From Chemical & Engineering News?

MR. SLATER: Exactly.

MR. FOWLER: Thank you, Doctor. It was nice meeting you virtually here.

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MR. SLATER: Thank you everybody.

THE VIDEOGRAPHER: The time is 12:39. This concludes the deposition.

[TIME NOTED: 12:39 p.m.]

_____

STEPHEN HECHT, Ph.D.

_____

Subscribed and sworn to before me this _____ day of _____, 2021.

_____

Notary Public

I N D E X

WITNESS	EXAMINATION BY	PAGE
HECHT	SLATER	405, 564
	FOWLER	495

E X H I B I T S

HECHT	DESCRIPTION	PAGE
Exhibit 27	Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry	413
Exhibit 28	Article by Wang	452
Exhibit 29	Article by Herron and Shank	460
Exhibit 30	Concise International Chemical Assessment Document 38	486
Exhibit 31	Article from Chemical & Engineering News	529
Exhibit 32	Hecht transcript from Tuttle v. Lorillard case	532
Exhibit 33	ICH M7 2017 edition	544

DIRECTIONS NOT TO ANSWER

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REQUESTS

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CERTIFICATION

I, TODD DeSIMONE, a Notary Public for and within the State of New York, do hereby certify:

That the witness whose testimony as herein set forth, was duly sworn by me; and that the within transcript is a true record of the testimony given by said witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 25th day of August, 2021.

Todd DeSimone
TODD DESIMONE

* * *

ERRATA SHEET
VERITEXT/NEW YORK REPORTING, LLC

CASE NAME: IN RE VALSARTAN
DATE OF DEPOSITION: 8/18/21
WITNESS' NAME: STEPHEN HECHT, Ph.D.

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STEPHEN HECHT, Ph.D.
SUBSCRIBED AND SWORN TO
BEFORE ME THIS______DAY
OF_______________, 2021.
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NOTARY PUBLIC
MY COMMISSION EXPIRES_________________